STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 134470

TO: Cybille Delacroix
Location: REM/3A78/3C70
Art Unit: 1614
Wednesday, October 06, 2004

Case Serial Number: 09/634369

From: Deirdre Arnold
Location: Biotech-Chem Library
REM 1A64
Phone: 571-272-2532

Deirdre.Arnold@uspto.gov

Search Notes

RUSH

This search targeted "eicosatrienoic" compounds and hypoxia. Results from some databases are limited by date (before 2000). Some duplication occurs between the subject search results and the inventor search results.

Please feel free to contact me if you have any questions or would like to amend the search.

Thank you for using STIC services.

Regards,
Deirdre Arnold

STIC SEARCH RESUL
FEEDBACK FORM

USPTO

Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contac*

Mary Hale, Information Branch Supervisor
571-272-2507 Remsen E01 D86

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* ☐ *Example: 1610*
- *Relevant prior art* ***found****, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technolog

  Types of relevant prior art found:
  - ☐ Foreign Patent(s)
  - ☐ Non-Patent Literature
    (journal articles, conference proceedings, new product announcements etc.)
- *Relevant prior art* ***not found****:*
  - ☐ Results verified the lack of relevant prior art (helped determine patentability)
  - ☐ Results were not useful in determining patentability or understanding the inventi

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library Remsen Bldg

sira
Search and Information Resources Administration

=> fil reg

FILE 'REGISTRY' ENTERED AT 12:28:06 ON 06 OCT 2004
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8
DICTIONARY FILE UPDATES: 4 OCT 2004 HIGHEST RN 756793-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil zcaplus

FILE 'ZCAPLUS' ENTERED AT 12:28:10 ON 06 OCT 2004
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FILE COVERS 1907 - 6 Oct 2004 VOL 141 ISS 15
FILE LAST UPDATED: 5 Oct 2004 (20041005/ED)

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=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 12:28:12 ON 06 OCT 2004
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for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.

FILE COVERS 1907 - 6 Oct 2004 VOL 141 ISS 15
FILE LAST UPDATED: 5 Oct 2004 (20041005/ED)

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=> fil medlin

FILE 'MEDLINE' ENTERED AT 12:28:16 ON 06 OCT 2004

FILE LAST UPDATED: 5 OCT 2004 (20041005/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil embase

FILE 'EMBASE' ENTERED AT 12:28:19 ON 06 OCT 2004

FILE COVERS 1974 TO 30 Sep 2004 (20040930/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

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=> fil biosis

FILE 'BIOSIS' ENTERED AT 12:28:23 ON 06 OCT 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 September 2004 (20040929/ED)

FILE RELOADED: 19 October 2003.

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 12:28:28 ON 06 OCT 2004

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 5 Oct 2004 (20041005/PD)
FILE LAST UPDATED: 5 Oct 2004 (20041005/ED)
HIGHEST GRANTED PATENT NUMBER: US6802078
HIGHEST APPLICATION PUBLICATION NUMBER: US2004194186
CA INDEXING IS CURRENT THROUGH 5 Oct 2004 (20041005/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 5 Oct 2004 (20041005/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

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=> fil toxcenter

FILE 'TOXCENTER' ENTERED AT 12:28:33 ON 06 OCT 2004
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FILE COVERS 1907 TO 5 Oct 2004 (20041005/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

=> fil pascal

FILE 'PASCAL' ENTERED AT 12:28:38 ON 06 OCT 2004

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FILE LAST UPDATED: 4 OCT 2004       <20041004/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
    IN THE BASIC INDEX (/BI) FIELD  <<<

=> fil caba

FILE 'CABA' ENTERED AT 12:28:41 ON 06 OCT 2004
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FILE COVERS 1973 TO 3 Sep 2004 (20040903/ED)

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substance identification.

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=> fil scisearch

FILE 'SCISEARCH' ENTERED AT 12:28:56 ON 06 OCT 2004
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FILE COVERS 1974 TO 2 Oct 2004 (20041002/ED)

=> fil mediconf

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FILE LAST UPDATED: 27 SEP 2004       <20040927/UP>

=> fil confsci

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FILE COVERS 1973 TO 23 Sep 2004 (20040923/ED)

=> fil wpix

FILE 'WPIX' ENTERED AT 12:29:11 ON 06 OCT 2004
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FILE LAST UPDATED:          1 OCT 2004      <20041001/UP>
MOST RECENT DERWENT UPDATE:     200463        <200463/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<
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>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

=> file stnguide

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  1, 2004 (20041001/UP).

=> d que l80
L1          1451 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIAO, J?/AU
L2            73 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ZELDIN, D?/AU
L3             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
L4             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PHARMACOLOGY/SC
L5               TRANSFER  PLU=ON  L4 1- RN :      20 TERMS
L6            20 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7            13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT MAN/CI
L8            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 NOT (CH3NO2 OR CH4N2O)/MF

L12         1656 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?EICOSATRIEN?/CNS
L13            6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (81276-02-0 OR 87173-81-7 OR
                 81276-03-1 OR 74868-37-4 OR 122087-32-5 OR 79551-82-9)/RN,CRN
L15          416 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
L16          278 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13
L17         7857 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L18        18537 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOXI?/CW
L19            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOXEM?/CW
L20            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANOXI?/CW
L21          192 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANOXEM?/CW
L22        18487 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOXIA+PFT,NT/CT
L23        18680 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "HYPOXIA, ANIMAL"+PFT,NT/CT
L24          553 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "HYPOXIA, PLANT"+PFT,NT/CT
L25          553 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PLANT STRESS (L) HYPOXIC"+PFT
                 ,NT/CT
L26          588 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANOXEMIA+PFT,NT/CT
L27        10767 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANOXIA+PFT,NT/CT
L28            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND (L18 OR L19 OR L20 OR
                 L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27)
L29            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 AND (L18 OR L19 OR L20 OR
                 L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27)
L30           22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND (L18 OR L19 OR L20 OR
                 L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27)
L31           22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L28 OR L29 OR L30)
L77        38939 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?OXYGEN? (3A) (?DEFICIEN? OR
                 LACK)
L78            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L77 AND (L15 OR L16)
L79           22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L78 OR L31
L80           15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L79 AND (AY<2000 OR PY<2000
                 OR PRY<2000)
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=> d que l76
L1          1451 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIAO, J?/AU
L2            73 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ZELDIN, D?/AU
L3             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
L4             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PHARMACOLOGY/SC
L5               TRANSFER  PLU=ON  L4 1- RN :      20 TERMS
L6            20 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7            13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT MAN/CI
L8            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 NOT (CH3NO2 OR CH4N2O)/MF

L13            6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (81276-02-0 OR 87173-81-7 OR
                 81276-03-1 OR 74868-37-4 OR 122087-32-5 OR 79551-82-9)/RN,CRN
L38          229 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8
L39          183 SEA FILE=MEDLINE ABB=ON  PLU=ON  L13
L40          780 SEA FILE=MEDLINE ABB=ON  PLU=ON  8,11,14-EICOSATRIENOIC
                 ACID+PFT,NT/CT
L41          455 SEA FILE=MEDLINE ABB=ON  PLU=ON  8,11,14-EICOSATRIENOIC ACID
                 (L) AA
L42        41302 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANOXIA+PFT,NT,RT/CT
L43         6614 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANOXEMIA+PFT,NT/CT
L44            4 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L38 OR L39 OR L40 OR L41)
                 AND (L42 OR L43)
L45        71771 SEA FILE=MEDLINE ABB=ON  PLU=ON  (?HYPOXIA? OR ?ANOXIA? OR
                 ?HYPOXEMIA? OR ?ANOXEMIA?)
L46            7 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L38 OR L39 OR L40 OR L41)
                 AND L45
L48           14 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 OR L13
L49              SEL  PLU=ON  L48 1- CHEM :      46 TERMS
L50          507 SEA FILE=MEDLINE ABB=ON  PLU=ON  L49
L51            8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L50 AND ((L42 OR L43) OR L45)

L52           12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L44 OR L46 OR L51
L72          983 SEA FILE=MEDLINE ABB=ON  PLU=ON  L50 OR (L40 OR L41)
L73         1530 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?OXYGEN? (3A) (?DEFICIEN? OR
                 LACK)
L74            1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L72 AND L73
L75           13 SEA FILE=MEDLINE ABB=ON  PLU=ON  L74 OR L52
L76            6 SEA FILE=MEDLINE ABB=ON  PLU=ON  L75 AND PY<2000


=> d que l71
L1          1451 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIAO, J?/AU
L2            73 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ZELDIN, D?/AU
L3             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
L4             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PHARMACOLOGY/SC
L5               TRANSFER  PLU=ON  L4 1- RN :      20 TERMS
L6            20 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7            13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT MAN/CI
L8            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 NOT (CH3NO2 OR CH4N2O)/MF

L13            6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (81276-02-0 OR 87173-81-7 OR
                 81276-03-1 OR 74868-37-4 OR 122087-32-5 OR 79551-82-9)/RN,CRN
L48           14 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 OR L13
L54              SEL  PLU=ON  L48 1- CHEM :      46 TERMS
L55          476 SEA FILE=EMBASE ABB=ON  PLU=ON  L54
L56           65 SEA FILE=EMBASE ABB=ON  PLU=ON  5,8,11 ICOSATRIENOIC ACID/CT
L57           65 SEA FILE=EMBASE ABB=ON  PLU=ON  5,8,11 ICOSATRIENOIC ACID+PFT,N
                 T/CT
L58          285 SEA FILE=EMBASE ABB=ON  PLU=ON  ICOSATRIENOIC ACID+PFT,NT/CT
L59         1274 SEA FILE=EMBASE ABB=ON  PLU=ON  ?ICOSATRIENO?
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L60       31819 SEA FILE=EMBASE ABB=ON  PLU=ON  HYPOXIA+PFT,NT/CT
L61       42724 SEA FILE=EMBASE ABB=ON  PLU=ON  HYPOXEMIA+PFT,NT/CT
L62        2268 SEA FILE=EMBASE ABB=ON  PLU=ON  ANOXIA+PFT,NT/CT
L63        8441 SEA FILE=EMBASE ABB=ON  PLU=ON  ANOXEMIA+PFT,NT/CT
L64       71245 SEA FILE=EMBASE ABB=ON  PLU=ON  (?HYPOXI? OR ?HYPOXEM? OR
                 ?ANOXI? OR ?ANOXEM?)
L65        1276 SEA FILE=EMBASE ABB=ON  PLU=ON  (L55 OR L56 OR L57 OR L58 OR
                 L59)
L66       72089 SEA FILE=EMBASE ABB=ON  PLU=ON  (L60 OR L61 OR L62 OR L63 OR
                 L64)
L67          19 SEA FILE=EMBASE ABB=ON  PLU=ON  L65 AND L66
L68         700 SEA FILE=EMBASE ABB=ON  PLU=ON  OXYGEN (3A) DEFICIEN?
L69           0 SEA FILE=EMBASE ABB=ON  PLU=ON  L65 AND L68
L70          19 SEA FILE=EMBASE ABB=ON  PLU=ON  L67 OR L69
L71           8 SEA FILE=EMBASE ABB=ON  PLU=ON  L70 AND (PY<2000 OR MY<2000)


=> d que l90
L1         1451 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIAO, J?/AU
L2           73 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ZELDIN, D?/AU
L3            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
L4            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PHARMACOLOGY/SC
L5              TRANSFER  PLU=ON  L4 1- RN :      20 TERMS
L6           20 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT MAN/CI
L8           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 NOT (CH3NO2 OR CH4N2O)/MF

L13           6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (81276-02-0 OR 87173-81-7 OR
                81276-03-1 OR 74868-37-4 OR 122087-32-5 OR 79551-82-9)/RN,CRN
L48          14 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 OR L13
L82             SEL  PLU=ON  L48 1- CHEM :     46 TERMS
L83         689 SEA FILE=BIOSIS ABB=ON  PLU=ON  L82
L84        4804 SEA FILE=BIOSIS ABB=ON  PLU=ON  (?OXYGEN? OR O2) (3A) (?DEFICIE
                 N? OR LACK OR ABSEN?)
L85       90375 SEA FILE=BIOSIS ABB=ON  PLU=ON  ?HYPOXI? OR ?HYPOXEM? OR
                 ?ANOXI? OR ?ANOXEM?
L86          11 SEA FILE=BIOSIS ABB=ON  PLU=ON  L83 AND (L84 OR L85)
L87        1592 SEA FILE=BIOSIS ABB=ON  PLU=ON  ?ICOSATRIEN?
L88          25 SEA FILE=BIOSIS ABB=ON  PLU=ON  L87 AND (L84 OR L85)
L89          25 SEA FILE=BIOSIS ABB=ON  PLU=ON  L86 OR L88
L90           8 SEA FILE=BIOSIS ABB=ON  PLU=ON  L89 AND (PY<2000 OR MY<2000)


=>

     (FILE 'USPATFULL, TOXCENTER' ENTERED AT 11:57:26 ON 06 OCT 2004)

=> d que l95
L1         1451 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIAO, J?/AU
L2           73 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ZELDIN, D?/AU
L3            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2
L4            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PHARMACOLOGY/SC
L5              TRANSFER  PLU=ON  L4 1- RN :      20 TERMS
L6           20 SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT MAN/CI
L8           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  L7 NOT (CH3NO2 OR CH4N2O)/MF

L13           6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (81276-02-0 OR 87173-81-7 OR
                81276-03-1 OR 74868-37-4 OR 122087-32-5 OR 79551-82-9)/RN,CRN
L48          14 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 OR L13
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L91          100 SEA L48
L92        19083 SEA (?OXYGEN? OR O2) (3A) (?DEFICIEN? OR LACK OR ABSEN?)
L93        53399 SEA ?HYPOXI? OR ?HYPOXEM? OR ?ANOXI? OR ?ANOXEM?
L94            4 SEA L91 AND (L92 OR L93)
L95            4 DUP REM L94 (0 DUPLICATES REMOVED)


=>

     (FILE 'PASCAL, CABA, SCISEARCH, MEDICONF, CONFSCI' ENTERED AT 12:01:54 ON
     06 OCT 2004)

=> d que l110
L100       11228 SEA (?OXYGEN? OR O2) (3A) (?DEFICIEN? OR LACK OR ABSEN?)
L101      114546 SEA ?HYPOXI? OR ?HYPOXEM? OR ?ANOXI? OR ?ANOXEM?
L105        2999 SEA (L96 OR L97 OR L98 OR L99) OR (L102 OR L103 OR L104)
L106          36 SEA L105 AND (L100 OR L101)
L107          31 DUP REM L106 (5 DUPLICATES REMOVED)
L108          30 SEA L105 (L) (L100 OR L101)
L109          25 SEA L107 AND L108
L110          22 SEA L109 AND (PY<2000 OR MY<2000)


=> d que l118
L112          98 SEA FILE=WPIX ABB=ON  PLU=ON  (?ICOSATRIEN? OR ?ICOSA TRIEN?
                 OR ?ICOS ATRIEN?)/BIX
L113        3494 SEA FILE=WPIX ABB=ON  PLU=ON  ((?OXYGEN? OR O2)(3A) (?DEFICIEN?
                  OR LACK OR ABSEN?))/BIX
L114        4620 SEA FILE=WPIX ABB=ON  PLU=ON  (?HYPOXI? OR ?ANOXI? OR ?HYPOXEM?
                  OR ?ANOXEM?)
L115        4666 SEA FILE=WPIX ABB=ON  PLU=ON  (?HYPOXI? OR ?ANOXI? OR ?HYPOXEM?
                  OR ?ANOXEM?)/BIX
L116         104 SEA FILE=WPIX ABB=ON  PLU=ON  (EET? OR DHET?)/BIX
L117         196 SEA FILE=WPIX ABB=ON  PLU=ON  L112 OR L116
L118           2 SEA FILE=WPIX ABB=ON  PLU=ON  L117 AND (L113 OR L114 OR L115)


=> dup rem l80 l76 l71 l90 l95 l118 l110
DUPLICATE IS NOT AVAILABLE IN 'MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

FILE 'HCAPLUS' ENTERED AT 12:31:23 ON 06 OCT 2004
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PROCESSING COMPLETED FOR L80
PROCESSING COMPLETED FOR L76
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L90
PROCESSING COMPLETED FOR L95
PROCESSING COMPLETED FOR L118
PROCESSING COMPLETED FOR L110
L121          45 DUP REM L80 L76 L71 L90 L95 L118 L110 (20 DUPLICATES REMOVED)
                 ANSWERS '1-15' FROM FILE HCAPLUS
                 ANSWERS '16-20' FROM FILE MEDLINE
                 ANSWERS '21-24' FROM FILE EMBASE
                 ANSWERS '25-26' FROM FILE USPATFULL
                 ANSWER '27' FROM FILE TOXCENTER
                 ANSWER '28' FROM FILE WPIX
                 ANSWERS '29-31' FROM FILE PASCAL
                 ANSWER '32' FROM FILE CABA
                 ANSWERS '33-45' FROM FILE SCISEARCH

=> d ibib abs hitstr hitind retable

L121 ANSWER 1 OF 45  HCAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2001:114981  HCAPLUS
DOCUMENT NUMBER:          134:173027
TITLE:                    Anti-inflammatory actions of cytochrome P450
                          epoxygenase-derived eicosanoids
INVENTOR(S):              Liao, James K.; Zeldin, Darryl
PATENT ASSIGNEE(S):       The Brigham and Women's Hospital, Inc., USA; National
                          Institutes of Health
SOURCE:                   PCT Int. Appl., 56 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2001010438         A1    20010215    WO 2000-US21744         20000810 <--
         W:  AU, CA, JP, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
     EP 1207877            A1    20020529    EP 2000-952688          20000810 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI, CY
PRIORITY APPLN. INFO.:                       US 1999-148434P      P  19990811 <--
                                             US 2000-634369       A2 20000809
```

WO 2000-US21744 W 20000810

AB Epoxyeicosatrienoic acids (EETs) are products of cytochrome P 450 epoxygenases that have vasodilatory properties similar to endothelium-derived hyperpolarizing factor (EDHF). The cytochrome P 450 isoform CYP2J2 was cloned and identified as a source of EETs in human endothelial cells. Physiol. concns. of EETs or overexpression of CYP2J2 decreased cytolcine-induced endothelial cell adhesion mol. expression and prevented subsequent leukocyte adhesion to the vascular wall by a mechanism involving inhibition of transcription factor NF-κB and IκB kinase (IKK). The inhibitory effects of EETs were independent of their membrane hypopolarizing effects suggesting that these mols. play an important non-vasodilatory role in vascular inflammation.

IT **97717-69-6D**, Epoxyeicosatrienoic acid, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

RN 97717-69-6 HCAPLUS
CN Eicosatrienoic acid, epoxy- (9CI) (CA INDEX NAME)

CM 1

CRN 97717-68-5
CMF C20 H38 O3
CCI IDS

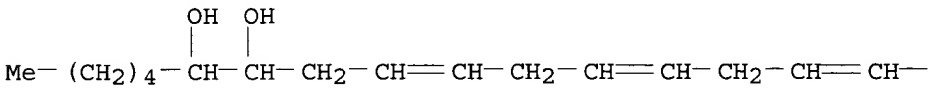
$HO_2C-(CH_2)_{18}-Me$

D1—O—D1

IT **79551-81-8 79551-82-9 81246-84-6**
81246-85-7 81276-02-0 81276-03-1
81920-20-9 81943-03-5 97717-69-6,
Epoxyeicosatrienoic acid **218461-95-1**, KMR-IV 87-27
325782-17-0, RKB-V 284-24
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

RN 79551-81-8 HCAPLUS
CN 5,8,11-Eicosatrienoic acid, 14,15-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

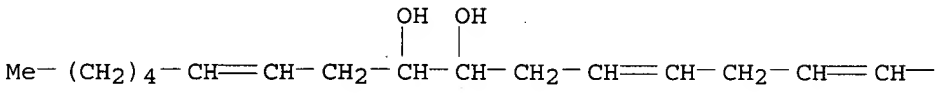


PAGE 1-B

— $(CH_2)_3$ — CO_2H

RN 79551-82-9 HCAPLUS
CN 5,8,14-Eicosatrienoic acid, 11,12-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

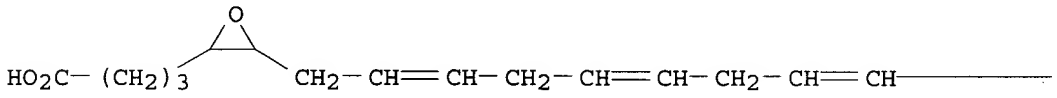


PAGE 1-B

— $(CH_2)_3$ — CO_2H

RN 81246-84-6 HCAPLUS
CN Oxiranebutanoic acid, 3-(2,5,8-tetradecatrienyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

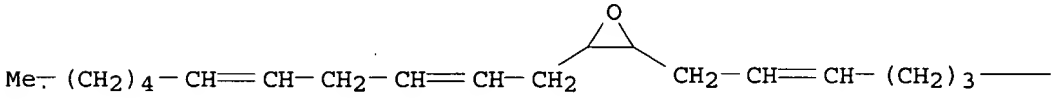


PAGE 1-B

— $(CH_2)_4$ — Me

RN 81246-85-7 HCAPLUS
CN 5-Heptenoic acid, 7-[3-(2,5-undecadienyl)oxiranyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

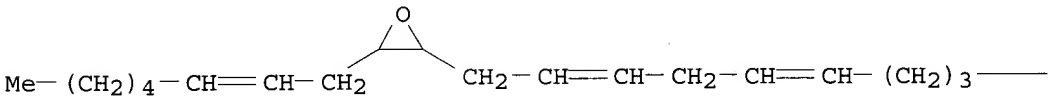


PAGE 1-B

—CO_2H

RN 81276-02-0 HCAPLUS
CN 5,8-Decadienoic acid, 10-[3-(2-octenyl)oxiranyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

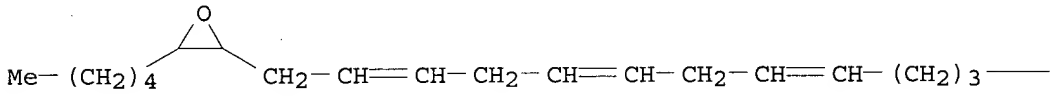


PAGE 1-B

—CO_2H

RN 81276-03-1 HCAPLUS
CN 5,8,11-Tridecatrienoic acid, 13-(3-pentyloxiranyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

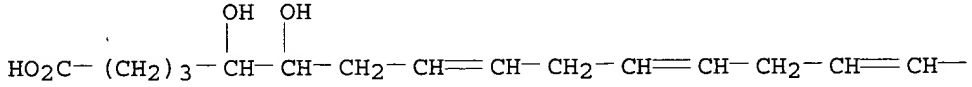


PAGE 1-B

—CO_2H

RN 81920-20-9 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, 5,6-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

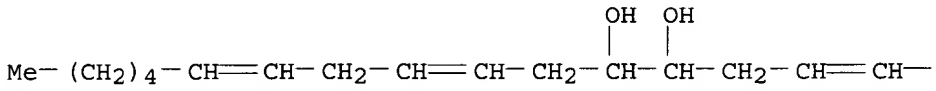


PAGE 1-B

— $(CH_2)_4$ — Me

RN 81943-03-5 HCAPLUS
CN 5,11,14-Eicosatrienoic acid, 8,9-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

— $(CH_2)_3$ — CO_2H

RN 97717-69-6 HCAPLUS
CN Eicosatrienoic acid, epoxy- (9CI) (CA INDEX NAME)

CM 1

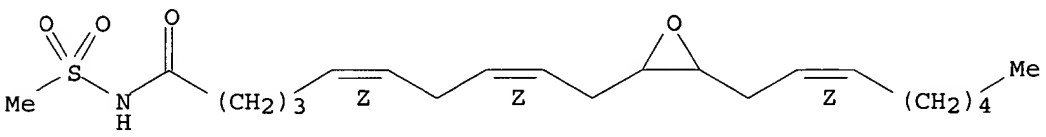
CRN 97717-68-5
CMF C20 H38 O3
CCI IDS

HO_2C — $(CH_2)_{18}$ — Me

D1 — O — D1

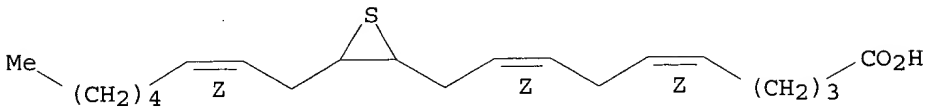
RN 218461-95-1 HCAPLUS
CN 5,8-Decadienamide, N-(methylsulfonyl)-10-[3-(2Z)-2-octenyloxiranyl]-, (5Z,8Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 325782-17-0 HCAPLUS
CN 5,8-Decadienoic acid, 10-[3-(2Z)-2-octenylthiiranyl]-, (5Z,8Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IC ICM A61K031-38
ICS A61K031-335
CC 1-7 (Pharmacology)
IT **Hypoxia, animal**
(prevention of cell death from reoxygenation following; anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)
IT **97717-69-6D**, Epoxyeicosatrienoic acid, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)
IT **79551-81-8 79551-82-9 81246-84-6 81246-85-7 81276-02-0 81276-03-1 81920-20-9 81943-03-5 97717-69-6**, Epoxyeicosatrienoic acid **218461-95-1**, KMR-IV 87-27 **325782-17-0**, RKB-V 284-24
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory actions of cytochrome P 450 epoxygenase-derived eicosanoids in combination with other agents)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Hammock	1999			US 5955496 A	HCAPLUS
Oltman	1998		932		

=> d ibib abs hitstr hitind retable 2-15

L121 ANSWER 2 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1999:335450 HCAPLUS
DOCUMENT NUMBER: 131:128581
TITLE: Hypoxia-induced production of 12-hydroxyeicosanoids in the corneal epithelium: involvement of a cytochrome P-4504B1 isoform
AUTHOR(S): Mastyugin, Vladimir; Aversa, Eleanor; Bonazzi, Albino; Vafaes, Christina; Mieyal, Paul; Schwartzman, Michal Laniado
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla, NY, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1999**), 289(3), 1611-1619
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

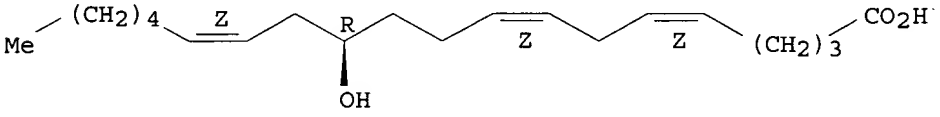
AB The corneal epithelium metabolizes arachidonic acid by a cytochrome P 450 (CYP)-mediated activity to 12-hydroxy-5,8,11,14-eicosatetraenoic acid (12(R)-HETE) and 12-hydroxy-5,8,14-eicosatrienoic acid (12(R)-HETrE). Both metabolites possess potent inflammatory properties, with 12(R)-HETrE being a powerful angiogenic factor, and they assume the role of inflammatory mediators in hypoxia- and chemical-induced injury in the cornea in vivo and in vitro. The authors used a model of corneal organ culture that exhibits hypoxia-induced epithelial CYP-dependent 12(R)-HETE and 12(R)-HETrE synthesis for isolating, identifying, and characterizing the CYP protein responsible for these eicosanoid syntheses. Northern anal. revealed the presence of a CYP4A-hybridizable mRNA, the levels of which were increased after hypoxia. Reverse transcription-polymerase chain reaction anal. with primers specific for the CYP4A family led to the isolation of a 671-base pair fragment with a 98.8% sequence homol. to the rabbit lung CYP4B1 isoform, of which the levels in the corneal epithelium were greatly increased under hypoxic conditions. Moreover, phenobarbital, an inducer of hepatic CYP4B1 in the rabbit, also induced 12-HETE and 12-HETrE synthesis. Antibodies against CYP4B1, but not against CYP4A1, inhibited hypoxia-, clofibrate-, and phenobarbital-induced 12-HETE and 12-HETrE synthesis. These results suggest the involvement of a CYP4B1 isoform in the corneal epithelial synthesis of these eicosanoids in response to hypoxia.

IT **117346-20-0**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(cytochrome P 4504B1 isoform expression in hypoxia-induced production of 12-hydroxyeicosanoids in corneal epithelium)

RN 117346-20-0 HCAPLUS

CN 5,8,14-Eicosatrienoic acid, 12-hydroxy-, (5Z,8Z,12R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT **Hypoxia, animal**
(cytochrome P 4504B1 isoform expression in hypoxia-induced production of 12-hydroxyeicosanoids in corneal epithelium)

IT 82337-46-0 **117346-20-0**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(cytochrome P 4504B1 isoform expression in hypoxia-induced production of 12-hydroxyeicosanoids in corneal epithelium)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abraham, N	1987	28	1464	Invest Ophthalmol Vi	HCAPLUS
Asakura, T	1992	187	455	Biochem Biophys Res	HCAPLUS
Asakura, T	1994	10	525	J Ocul Pharmacol	HCAPLUS
Bylund, J	1998	284	51	J Pharmacol Exp Ther	HCAPLUS

Capdevila, J	1981	101	1357	Biochem Biophys Res	HCAPLUS
Capdevila, J	1986	141	1007	Biochem Biophys Res	HCAPLUS
Chomczynski, P	1987	162	156	Anal Biochem	HCAPLUS
Claire, A	1997	28	351	Gen Pharmacol	
Conners, M	1995	36	828	Invest Ophthalmol Vi	MEDLINE
Conners, M	1995	36	841	Invest Ophthalmol Vi	MEDLINE
Conners, M	1997	38	1963	Invest Ophthalmol Vi	MEDLINE
Das, N	1981	33	525	Exp Eye Res	HCAPLUS
Devchand, P	1996	384	39	Nature (London)	HCAPLUS
Ding, X	1991	285	120	Arch Biochem Biophys	HCAPLUS
Falck, J	1990	265	10244	J Biol Chem	HCAPLUS
Forman, B	1995	83	803	Cell	HCAPLUS
Gasser, R	1989	35	617	Mol Pharmacol	HCAPLUS
Helferich, W	1991	40	674	Mol Pharmacol	HCAPLUS
Johnson, E	1990	29	873	Biochem J	HCAPLUS
Kishida, K	1986	5	529	Curr Eye Res	HCAPLUS
Kocarek, T	1993	29	A62	In Vitro Cell Dev Bi	
Laethem, R	1994	1206	42	Biochim Biophys Acta	HCAPLUS
Laethem, R	1992	42	958	Mol Pharmacol	HCAPLUS
Laniado Schwartzman, M	1997		3	Advances in Ocular T	
Lin, F	1995	269	F806	Am J Physiol	HCAPLUS
Lin, M	1993	190	1122	Biochem Biophys Res	HCAPLUS
Maslansy, C	1982	18	683	In Vitro	
Matsumoto, K	1987	6	847	Curr Eye Res	HCAPLUS
Murphy, R	1988	263	17197	J Biol Chem	HCAPLUS
Nhamburo, P	1989	28	8060	Biochemistry	HCAPLUS
Nishimura, M	1991	290	326	Arch Biochem Biophys	HCAPLUS
Okamoto, T	1993	197	878	Biochem Biophys Res	MEDLINE
Okino, S	1985	82	5310	Proc Natl Acad Sci U	HCAPLUS
Oliw, E	1982	257	3771	J Biol Chem	HCAPLUS
Paine, A	1976	158	109	Biochem J	HCAPLUS
Richardson, T	1995	323	87	Arch Biochem Biophys	HCAPLUS
Rifkind, A	1995	320	380	Arch Biochem Biophys	HCAPLUS
Schwartzman, M	1987	252	635	Arch Biochem Biophys	HCAPLUS
Schwartzman, M	1987	6	623	Curr Eye Res	HCAPLUS
Shichi, H	1991	10	779	Curr Eye Res	MEDLINE
Shichi, H	1969	8	60	Exp Eye Res	HCAPLUS
Shichi, H	1975	21	557	Exp Eye Res	HCAPLUS
Shichi, H	1996	37	S800	Invest Ophthalmol Vi	
Vafeas, C	1998	287	903	J Pharmacol Exp Ther	HCAPLUS
Wang, M	1996	336	240	Arch Biochem Biophys	HCAPLUS
Wang, M	1996	334	380	Arch Biochem Biophys	HCAPLUS
Yamamoto, S	1994	1210	217	Biochim Biophys Acta	HCAPLUS
Yu, K	1995	270	23975	J Biol Chem	HCAPLUS
Zeldin, D	1995	95	2150	J Clin Invest	HCAPLUS
Zhao, C	1995	60	143	Exp Eye Res	HCAPLUS

L121 ANSWER 3 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2000:234359 HCAPLUS

DOCUMENT NUMBER: 133:99886

TITLE: Lack of evidence for the involvement of cytochrome P450 mono-oxygenase-dependent metabolites of arachidonic acid and cannabinoids in endothelium-dependent relaxations of the guinea-pig basilar artery

AUTHOR(S): Petersson, Jesper; Zygmunt, Peter M.; Sorgard, Morten; Movahed, Pouya; Hogestatt, Edward D.

CORPORATE SOURCE: Department of Clinical Pharmacology, Lund University Hospital, Lund, S-221 85, Swed.

SOURCE: Endothelium-Dependent Hyperpolarizations, [Proceedings

of the International Symposium on Endothelium-Derived Hyperpolarizing Factor], 2nd, Vaux de Cernay, France, June 5-6, 1998 (**1999**), Meeting Date 1998, 37-46. Editor(s): Vanhoutte, Paul M. Harwood Academic Publishers: Amsterdam, Neth.
CODEN: 68TZAU
DOCUMENT TYPE: Conference
LANGUAGE: English

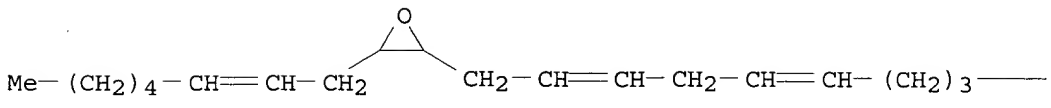
AB In the guinea-pig basilar artery, both endothelium-derived hyperpolarizing factor (EDHF) and NO contribute to endothelium-dependent relaxations. In this artery, the EDHF-mediated relaxation is totally inhibited by a combination of charybdotoxin plus apamin, whereas the NO-mediated vasodilatation is abolished by the guanylate cyclase inhibitor ODQ or the NO synthase inhibitor Nω-nitro-L-Arg. The identity of EDHF in the guinea-pig basilar artery, however, remains to be determined The epoxyeicosatrienoic acids, which are derivs. of arachidonic acid formed by cytochrome P 450-dependent monoxygenase, act as endothelium-derived hyperpolarizing factors in some vascular tissues. In the guinea-pig basilar artery, 17-octadecynoic acid, which is considered a selective inhibitor of cytochrome P 450 monoxygenase, and 5,8,11,14-eicosatetraynoic acid, a non-selective inhibitor of arachidonic acid metabolism, were unable to antagonize the EDHF-mediated relaxation induced by acetylcholine in the guinea-pig basilar artery. Furthermore, 11,12-epoxyeicosatrienoic acid did not produce a relaxing response under conditions when EDHF causes vasodilatation. NO synthase and cytochrome P 450 monoxygenase show similar sensitivity to oxygen. In the present study, relaxations mediated by endothelium-derived NO were abolished under hypoxic conditions (PO2 = 6 mm Hg), whereas EDHF-mediated relaxations were almost intact. In contrast to the endogenous NO response, the NO donor S-nitroso-N-acetylpenicillamine induced a concentration-dependent relaxation during hypoxia.

Endocannabinoids such as anandamide (arachidonoylethanolamide) may participate in regulation of vascular tone. Anandamide, acting at cannabinoid receptors (CB1), was proposed as a candidate for EDHF in the rat isolated perfused mesenteric vascular bed. In the guinea-pig basilar artery, anandamide induced concentration-dependent relaxations, which were partially inhibited by the selective CB1 receptor antagonist SR141716. In contrast, SR141716 had no effect on the EDHF-mediated response induced by acetylcholine. Furthermore, the combination of charybdotoxin and apamin did not affect anandamide-induced relaxations in the guinea-pig basilar artery, whereas EDHF-mediated responses were abolished. 2 Other endogenous cannabinoid receptor ligands, 2-arachidonoylglycerol and palmitoylethanolamide, were devoid of relaxant effect. The results of the present study suggest that EDHF is not a cytochrome P 450 monoxygenase-dependent arachidonic acid metabolite such as epoxyeicosatrienoic acid or the endocannabinoid anandamide in the guinea-pig basilar artery.

IT **81276-02-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(no evidence for involvement of cytochrome P 450 monoxygenase-dependent metabolites in endothelium-dependent relaxations of basilar artery)

RN 81276-02-0 HCAPLUS
CN 5,8-Decadienoic acid, 10-[3-(2-octenyl)oxiranyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

— CO_2H

CC 2-8 (Mammalian Hormones)

IT **Hypoxia, animal**
Vasodilation
(no evidence for involvement of cytochrome P 450 monoxygenase-dependent metabolites in endothelium-dependent relaxations of basilar artery)

IT 1191-85-1, 5,8,11,14-Eicosatetraynoic acid 9035-51-2, Cytochrome P450, biological studies 24345-16-2, Apamin 34450-18-5, 17-Octadecynoic acid **81276-02-0** 94421-68-8, Anandamide 95751-30-7, Charybdotoxin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(no evidence for involvement of cytochrome P 450 monoxygenase-dependent metabolites in endothelium-dependent relaxations of basilar artery)

L121 ANSWER 4 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1999:38027 HCAPLUS
DOCUMENT NUMBER: 130:221598
TITLE: Hypoxia stimulates the synthesis of cytochrome p450-derived inflammatory eicosanoids in rabbit corneal epithelium
AUTHOR(S): Vafeas, Christina; Mieyal, Paul A.; Urbano, Ferdinando; Falck, John R.; Chauhan, Kamlesh; Berman, Michael; Schwartzman, Michal Laniado
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla, NY, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1998**), 287(3), 903-910
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

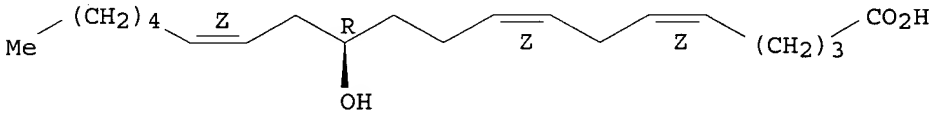
AB The corneal epithelium metabolizes arachidonic acid by a cytochrome P 450-(CYP) mediated pathway to 12(R)hydroxy-5,8, 10, 14-eicosatrienoic acid [12(R)-HETE] and 12(R)hydroxy-5,8, 14-eicosatrienoic acid [12(R)-HETrE]. Both metabolites possess potent inflammatory properties with 12(R)-HETrE being a powerful angiogenic factor and assume the role of inflammatory mediators in hypoxia- and chemical-induced injury in the cornea, in vivo. We developed an in vitro model of corneal organ culture to characterize the biochem. and mol. events involved in the increased synthesis of these metabolites. These cultured corneas exhibit epithelial cytochrome P 450 CYP-dependent 12(R)-HETE and 12(R)-HETrE synthesis as indicated by chiral anal. and by the ability of CYP enzyme inhibitors to repress their synthesis. Hypoxia greatly and selectively stimulated the synthesis of 12(R)-HETE (7-fold over control normoxic conditions) and 12(R)-HETrE. The

bacterial endotoxin, lipopolysaccharide, also increased the synthesis of these eicosanoids, substantiating the notion that this activity may function as an inflammatory pathway. These metabolites were detected in the culture medium by gas chromatog./mass spectroscopy (GC/MS) anal. and their levels significantly increased in hypoxia-treated corneas, further indicating their endogenous formation in response to injury. This in vitro model provides an excellent preparation for studying factors regulating the synthesis of these inflammatory eicosanoids and for isolating, identifying and characterizing the CYP protein responsible for their synthesis.

IT **117346-20-0**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(cytochrome P 450-derived inflammatory eicosanoids formation response to hypoxia in rabbit corneal epithelium)

RN 117346-20-0 HCAPLUS
CN 5,8,14-Eicosatrienoic acid, 12-hydroxy-, (5Z,8Z,12R,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



CC 14-10 (Mammalian Pathological Biochemistry)

IT Disease models
Hypoxia, animal
Inflammation
(cytochrome P 450-derived inflammatory eicosanoids formation response to hypoxia in rabbit corneal epithelium)

IT 82337-46-0 **117346-20-0**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(cytochrome P 450-derived inflammatory eicosanoids formation response to hypoxia in rabbit corneal epithelium)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Asakura, T	1994	10	525	J Ocul Pharm	HCAPLUS
Bacon, K	1988	95	966	Br J Pharmacol	HCAPLUS
Bradford, M	1976	72	248	Anal Biochem	HCAPLUS
Camp, R	1988	94	1043	Br J Pharmacol	MEDLINE
Camp, R	1993	26	431	Prostaglandins	
Capdevila, J	1988	261	257	Arch Biochem Biophys	HCAPLUS
Capdevila, J	1986	141	1007	Biochem Biophys Res	HCAPLUS
Carlson, T	1996	49	796	Mol Pharmacol	HCAPLUS
Chen, J	1995	47	940	Mol Pharmacol	HCAPLUS
Chen, Y	1992	44	137	Biochem Pharmacol	HCAPLUS
Cho, H	1991	34	1503	J Med Chem	HCAPLUS
Conners, M	1995	36	828	Invest Ophthalmol Vi	MEDLINE
Conners, M	1997	38	1963	Invest Ophthalmol Vi	MEDLINE
Conners, M	1994	104	1	J Invest Dermatol	
Conners, M	1996	12	19	J Ocular Pharmacol T	HCAPLUS

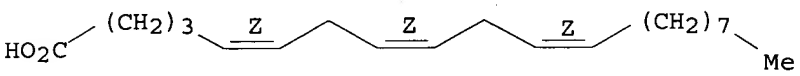
Cunningham, F	1987	34	71	Prostaglandins	HCAPLUS
Holden, B	1989	66	717	Optom Vis Sci	MEDLINE
Holtzman, M	1989	84	1446	J Clin Invest	HCAPLUS
Hurst, J	1991	266	6726	J Biol Chem	HCAPLUS
Husted, R	1997	38	S284	Invest Ophthalmol Vi	
Khatsenko, O	1993	90	11147	Proc Natl Acad Sci U	HCAPLUS
Laniado Schwartzman, M	1997		3	Advances in Ocular T	
Laniado Schwartzman, M	1991	180	445	Biochem Biophys Res	
Lin, M	1993	190	1122	Biochem Biophys Res	HCAPLUS
Mastyugin, V	1998	39	1019	Invest Ophthalmol Vi	
Morgan, E	1993	45	415	Biochem Pharmacol	HCAPLUS
Moscona, A	1965		80	Cells and Tissues in	
Nishimura, M	1991	290	326	Arch Biochem Biophys	HCAPLUS
Ortiz de Montellano, P	1984	259	4136	J Biol Chem	HCAPLUS
Paine, A	1991	72	349	Int J Exp Pathol	MEDLINE
Proctor, K	1989	26	53	Blood Vessels	MEDLINE
Schwartzman, M	1987	84	8125	Proc Natl Acad Sci U	HCAPLUS
Sewer, M	1997	280	1445	J Pharmacol Exp Ther	HCAPLUS
Shin, D	1989	30	3923	Tetrahedron Lett	HCAPLUS
Stoltz, R	1994	10	307	J Ocul Pharm	HCAPLUS
Thurman, R	1980	31	229	Pharmacol Rev	
Van Wauwe, J	1991	4	155	Eicosanoids	HCAPLUS
Wainwright, S	1990	29	10126	Biochemistry	HCAPLUS
Waring, G	1987	31	262	Surv Ophthalmol	
Williams, K	1988	156	101	J Pathol	HCAPLUS
Woollard, P	1986	136	169	Biochem Biophys Res	HCAPLUS
Woollard, P	1988	118	277	Brit J Dermatol	
Yamamoto, S	1994	1210	217	Biochim Biophys Acta	HCAPLUS

L121 ANSWER 5 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1987:422440 HCAPLUS
DOCUMENT NUMBER: 107:22440
TITLE: Decreased pulmonary vascular responsiveness in rats raised on an essential fatty acid-deficient diet
AUTHOR(S): Morganroth, M. L.; Pickett, W. C.; Worthen, S.; Mathias, M.; Reeves, J. T.; Voelkel, N. F.
CORPORATE SOURCE: Med. Cent., Univ. Michigan, Ann Arbor, MI, 48109-0360, USA
SOURCE: Prostaglandins (**1987**), 33(2), 181-97
CODEN: PRGLBA; ISSN: 0090-6980
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rats raised on an essential fatty acid-deficient diet (EFAD) had decreased esterified plasma arachidonic acid and increased 5,8,11-eicosatrienoic acid compared to rats raised on the normal diet (control). Compared to the time-matched responses in control isolated perfused lungs, the pressor responses to angiotensin II and alveolar hypoxia were blunted in lungs from the arachidonate-deficient rats. This decreased pulmonary vascular responsiveness was not affected by the addition of indomethacin or arachidonic acid to the lung perfusate. Similarly, the pulmonary artery rings from arachidonate-deficient rats demonstrated decreased reactivity to norepinephrine compared to rings from control rats. In contrast, the tension increases to norepinephrine were greater in aortic rings from the arachidonate-deficient rats compared to control. Stimulated lung tissue from the arachidonate-deficient animals produced less slow-reacting substance and platelet-activating factor-like material but the same amount of 6-kteo-PGF1α and TXB2 compared to control lungs. Thus, there is an association between altered vascular responsiveness and impairment of stimulated production of slow-reacting substance and platelet-activating factor-like material in rats raised on an EFAD diet.

IT **20590-32-3**, 5,8,11-Eicosatrienoic acid
RL: BIOL (Biological study)
(of blood, essential fatty acid deficiency effect on)
RN 20590-32-3 HCAPLUS
CN 5,8,11-Eicosatrienoic acid, (5Z,8Z,11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



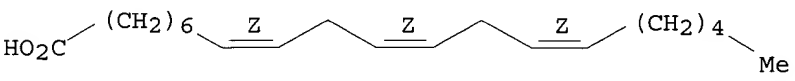
CC 18-5 (Animal Nutrition)
IT **Hypoxia**
(pulmonary vascular responsiveness in, in essential fatty acid deficiency)
IT **20590-32-3**, 5,8,11-Eicosatrienoic acid
RL: BIOL (Biological study)
(of blood, essential fatty acid deficiency effect on)

L121 ANSWER 6 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:582122 HCAPLUS
DOCUMENT NUMBER: 132:121920
TITLE: Effect of dietary flax oil and hypobaric hypoxia on pulmonary hypertension and haematological variables in broiler chickens
AUTHOR(S): Walton, J.-P.; Bond, J. M.; Julian, R. J.; Squires, E. J.
CORPORATE SOURCE: Department of Animal and Poultry Science, University of Guelph, Guelph, ON, N1G 2W1, Can.
SOURCE: British Poultry Science (**1999**), 40(3), 385-391
CODEN: BPOSA4; ISSN: 0007-1668
PUBLISHER: Carfax Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three expts. were conducted with broiler chickens using hypobaric chambers and diets containing 25 or 50 g flax (linseed) oil/kg feed or control diets with equivalent amts. of animal/vegetable (A/V) blend oil for 4 wk. The effects of these diets on hematol. variables and the extent of heart right ventricular hypertrophy (RVH) leading to ascites were determined The overall growth rate was not consistently affected by the diets, although feeding 25 g flax oil/kg decreased the weight gain in week 4 in one experiment Feeding 50 g flax oil/kg, but not 25 g flax oil/kg, decreased the RVH in birds exposed to hypobaric conditions compared to birds fed control diets. Feeding 50 g flax oil/kg under hypobaric conditions decreased the hematocrit and Hb values, increased erythrocyte deformability and proportion of unsatd. fatty acids in erythrocyte membranes, and decreased the whole blood viscosity compared to birds fed control diets. These effects were not seen in birds fed 25 g flax oil/kg feed. The n-3/n-6 fatty acid ratio in erythrocyte membranes was increased in the 50 g flax oil/kg group vs. controls. Thus, feeding 50 g flax oil/kg feed can decrease RVH in broiler chickens. This may be attributed to increased erythrocyte deformability due to increased proportion of unsatd. fatty acids in erythrocyte membranes.
IT **1783-84-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(dietary flax oil and hypobaric hypoxia effects on heart hypertrophy, pulmonary hypertension and hematol. values in broiler chickens)

RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



CC 18-5 (Animal Nutrition)
Section cross-reference(s): 14
IT Chicken (Gallus domesticus)
Hypoxia, animal
Nutrition, animal
(dietary flax oil and hypobaric hypoxia effects on heart hypertrophy, pulmonary hypertension and hematol. values in broiler chickens)
IT 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 112-85-6, Docosanoic acid 463-40-1 506-30-9, Eicosanoic acid 506-32-1 544-63-8, Tetradecanoic acid, biological studies 557-59-5, Tetracosanoic acid **1783-84-2** 2416-19-5 5561-99-9 5598-38-9 6217-54-5 10417-94-4 24880-45-3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary flax oil and hypobaric hypoxia effects on heart hypertrophy, pulmonary hypertension and hematol. values in broiler chickens)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Archer, S	1989	66	1662	Journal of Applied P	HCAPLUS
Berlin, E	1992	3	392	Journal of Nutrition	HCAPLUS
Bhatty, R	1995		22	Flaxseed in Human Nu	HCAPLUS
Bond, J	1996	37	731	British Poultry Scie	HCAPLUS
Bond, J	1997	77	279	Canadian Journal of	HCAPLUS
Calder, P	1992	75	108	Immunology	HCAPLUS
Diaz, G	1994	23	91	Avian Pathology	HCAPLUS
Guthrie, A	1987	54	599	Onderstepoort Journa	MEDLINE
Hakim, T	1988	25	857	Biorheology	MEDLINE
Holub, B	1995		128	Flaxseed in Human Nu	HCAPLUS
Huchzermeyer, F	1986	119	94	Veterinary Record	MEDLINE
Hulan, H	1989	68	153	Poultry Science	HCAPLUS
Julian, R	1993	22	419	Avian Pathology	
Julian, R	1986		608	Proceedings of the 4	
Maxwell, M	1986	15	511	Avian Pathology	
Maxwell, M	1986	15	524	Avian Pathology	
Maxwell, M	1990	19	23	Avian Pathology	
Mirsalimi, S	1991	35	374	Avian Diseases	MEDLINE
Mirsalimi, S	1993	37	660	Avian Diseases	MEDLINE
Mohandes, N	1980	66	563	Journal of Clinical	
Monge, C	1991	71	1135	Physiological Review	MEDLINE
Nair, S	1997	127	383	Journal of Nutrition	HCAPLUS
Needleman, P	1979	76	944	Proceedings of the N	HCAPLUS
Owen, R	1990	34	754	Avian Diseases	MEDLINE
SAS Institute	1985			User's Guide: Statis	
Sillau, A	1980	386	269	Pflugers Archiv	MEDLINE

Wallace, J	1997	214	192	Proceedings of the S	HCAPLUS
Wideman, R	1994		185	Proceedings Arkansas	

L121 ANSWER 7 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:251045 HCAPLUS
DOCUMENT NUMBER: 128:292260
TITLE: Use of essential fatty acids for the treatment and prevention of radiotherapy-associated radiation damage to erythrocytes
INVENTOR(S): Horrobin, David Frederick; Scott, Catherine Ann
PATENT ASSIGNEE(S): Scotia Holdings PLC, UK; Horrobin, David Frederick; Scott, Catherine Ann
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

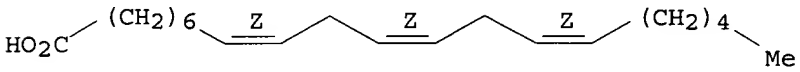
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9816215	A1	19980423	WO 1997-GB2441	19970911 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9708226	A	19980511	ZA 1997-8226	19970912 <--
PRIORITY APPLN. INFO.:			GB 1996-21373 A	19961014 <--

AB The use is disclosed of ≥1 n-6 essential fatty acid and/or ≥1 n-3 essential fatty acid in the preparation of a medicament for countering red cell damage and/or tissue hypoxia during radiotherapy, and/or consequent fatigue.

IT **1783-84-2**, Dihomo-γ-linolenic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(essential fatty acids for treatment and prevention of radiotherapy-associated radiation damage to erythrocyte)

RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IC ICM A61K031-20
CC 8-9 (Radiation Biochemistry)
IT Fatigue, biological
Hypoxia, animal
(essential fatty acids for treatment and prevention of radiotherapy-associated radiation damage to erythrocyte and fatigue and tissue hypoxia)
IT 60-33-3, Linoleic acid, biological studies 463-40-1, α-Linolenic

acid 506-26-3, γ-Linolenic acid 506-32-1, Arachidonic acid **1783-84-2**, Dihomo-γ-linolenic acid 6217-54-5, Docosahexaenoic acid 10417-94-4, Eicosapentaenoic acid 20290-75-9, Stearidonic acid 24880-45-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(essential fatty acids for treatment and prevention of radiotherapy-associated radiation damage to erythrocyte)

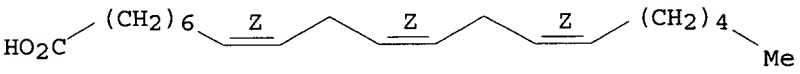
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baronzio, G	1994	14	1145	ANTICANCER RESEARCH	
Efamol Holdings Plc	1991			EP 0416855 A	HCAPLUS
Horrobin, D	1991	35	23	MEDICAL HYPOTHESES	HCAPLUS
Mevetek Ab J B	1996			SE 9402338 A	HCAPLUS
Mochida Pharm Co Ltd	1983			JP 58180423 A	HCAPLUS
Rybczynska, M	1990	58	313	INTERNATIONAL JOURNA	HCAPLUS
Scotia Holdings Plc	1994			EP 0609064 A	HCAPLUS
Yonei, S	1984	46	463	INTERNATIONAL JOURNA	HCAPLUS

L121 ANSWER 8 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:491010 HCAPLUS
DOCUMENT NUMBER: 129:108480
TITLE: Polyunsaturated fatty acids influence prostanoid synthesis in vascular endothelial cells under hypoxia and reoxygenation
AUTHOR(S): Oudot, Fabien; Cordelet, Catherine; Sergiel, Jean Pierre; Grynberg, Alain
CORPORATE SOURCE: Faculte Sciences Pharmaceutiques Biologiques, Paris, F-75270, Fr.
SOURCE: International Journal for Vitamin and Nutrition Research (**1998**), 68(4), 263-271
CODEN: IJVNAP; ISSN: 0300-9831
PUBLISHER: Hogrefe & Huber Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the influence of membrane polyunsatd. fatty acids (PUFA) on prostanoid metabolism in the vascular endothelium, in pathophysiol. conditions. 2 Models of cultured endothelial cells were used, from bovine aorta (BAEC) and human umbilical vein (HUVEC). In physiol. conditions, the main prostanoids were prostacyclin and PGE2 in the BAEC and prostacyclin and PGF2α in the HUVEC. Reoxygenation (2.5 h) but not hypoxia (2.5 h) enhanced prostanoid synthesis in both models. Cell enrichment with arachidonic acid (AA, n-6 cells) increased both AA and C22:4 n-6 and decreased n-3 PUFAs in the phospholipids. Conversely enrichment with eicosapentaenoic and docosahexaenoic acids (EPA and DHA, n-3 cells) increased the n-3 PUFAs and decreased the n-6 PUFAs. The BAEC incorporated more PUFA in the phospho-lipids than the HUVEC. In the n-3 cells, EPA incorporation was higher than that of DHA. Increasing AA increased the production of both prostacyclin and PGF2α by the BAEC and only that of PGF2α by the HUVEC. Increasing n-3 PUFA decreased the release of PGE2 and TxA2 by the BAEC and only that of prostacyclin by the HUVEC. In the n-6 cells, hypoxia became a stimulus for prostanoid production and the stimulating effect of reoxygenation was reinforced in the HUVEC whereas it was abolished in the BAEC. N-3 PUFA blocked the reoxygenation-stimulated production These results suggest a strong importance of dietary PUFA in the response of vascular endothelium to pathol. conditions.

IT **1783-84-2**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(polyunsatd. fatty acids effect on prostanoid synthesis in vascular endothelium under hypoxia and reoxygenation)
RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



CC 18-5 (Animal Nutrition)
Section cross-reference(s): 13, 14
IT **Hypoxia, animal**
(polyunsatd. fatty acids effect on prostanoid synthesis in vascular endothelium under hypoxia and reoxygenation)
IT 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies 506-32-1 **1783-84-2** 6217-54-5 10417-94-4 25182-74-5 28874-58-0
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(polyunsatd. fatty acids effect on prostanoid synthesis in vascular endothelium under hypoxia and reoxygenation)

L121 ANSWER 9 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:34785 HCAPLUS
DOCUMENT NUMBER: 128:152010
TITLE: Effects of hypoxia and low temperature on substrate fluxes in fish: plasma metabolite concentrations are misleading
AUTHOR(S): Haman, Francois; Zwingelstein, Georges; Weber, Jean-Michel
CORPORATE SOURCE: Biology Department, University Ottawa, Ottawa, ON, K1N 6N5, Can.
SOURCE: American Journal of Physiology (**1997**), 273(6, Pt. 2), R2046-R2054
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Oxygen levels and temperature can fluctuate rapidly in aquatic environments. Even though the effects of environmental stresses on fish metabolism have been studied extensively, information on fuel kinetics is extremely limited because it relies almost exclusively on changes in substrate concns. The turnover rate of nonesterified fatty acids (NEFA) has never been measured in fish. Therefore, our goal was to quantify glucose and NEFA fluxes in rainbow trout acutely exposed to severe hypoxia (25% O2 saturation) or low temperature (6° for fish acclimated to 15°) by performing continuous infusions of 6-[3H]glucose and 1-[14C]palmitate in vivo. Results show that hypoxia causes a 53% decrease in hepatic glucose production, whereas a rapid drop in temperature induces equivalent declines in glucose, NEFA, and oxygen fluxes [temperature coefficient .simeq. 2]. More importantly, kinetic

changes in glucose and NEFA fluxes are not accompanied by interpretable changes in the plasma concns. of these metabolites. Thus using concentration changes to draw conclusions about fluxes must be avoided.

IT **80558-45-8**, Eicosatrienoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypoxia and low temperature effects on substrate fluxes in fish)

RN 80558-45-8 HCAPLUS
CN Eicosatrienoic acid, (Z,Z,Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 506-30-9
CMF C20 H40 O2

$HO_2C-(CH_2)_{18}-Me$

CC 12-6 (Nonmammalian Biochemistry)

IT **Hypoxia, animal**
Liver
Oncorhynchus mykiss
(hypoxia and low temperature effects on substrate fluxes in fish)

IT 50-99-7, D-Glucose, biological studies 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 506-32-1 7782-44-7, Oxygen, biological studies 27104-13-8 27213-43-0, Octadecatrienoic acid 28039-99-8 28933-89-3 28984-77-2 32839-18-2, Docosahexaenoic acid 32839-28-4, Eicosadienoic acid 32839-30-8 32839-34-2 **80558-45-8**, Eicosatrienoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypoxia and low temperature effects on substrate fluxes in fish)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bergmeyer, H	1985			Methods of Enzymatic	
Boutilier, R	1988	71	69	Respir Physiol	MEDLINE
Cameron, J	1989			The Respiratory Phys	
Carlson, M	1991	261	E815	Am J Physiol, Endocr	
Crawshaw, L	1984	246	R439	Am J Physiol, Regula	
Davis, J	1975	32	2295	J Fish Res Board Can	
Dunn, J	1987	65	1144	Can J Zool	HCAPLUS
Dunn, J	1986	123	229	J Exp Biol	HCAPLUS
Fritsche, R	1993		181	Fish Ecophysiology	
Guderley, H	1990	259	R245	Am J Physiol, Regula	
Hagenfeldt, L	1975	34	2236	Federation Proc	
Haman, F	1996	199	1157	J Exp Biol	HCAPLUS
Hazel, J	1984	246	R460	Am J Physiol, Regula	
Hazel, J	1993		427	The Physiology of Fi	
Heath, A	1965	38	325	Physiol Zool	HCAPLUS
Henderson, R	1987	26	281	Prog Lipid Res	HCAPLUS
Hochachka, P	1984			Biochemical Adaptati	
Holeton, G	1967	46	317	J Exp Biol	MEDLINE
McClelland, G	1995	30	147	Lipids	HCAPLUS
Migliorini, R	1992	263	R857	Am J Physiol, Regula	
Paul, P	1967	22	615	J Appl Physiol	HCAPLUS
Perry, S	1989	67	2961	Can J Zool	
Plisetskaya, E	1980	5	273	Env Biol Fish	HCAPLUS

Randall, D	1982	100	275	J Exp Biol	
Randle, P	1963	1	785	Lancet	MEDLINE
Sidell, B	1987	129	191	J Exp Biol	HCAPLUS
Steele, R	1959	82	420	Ann NY Acad Sci	HCAPLUS
Steffensen, J	1989	6	49	Fish Physiol Biochem	
Tserng, K	1981	22	852	J Lipid Res	HCAPLUS
van Den Thillart, G	1982	2	49	Mol Physiol	HCAPLUS
van Raaij, M	1995	268	R1163	Am J Physiol, Regula	
van Raaij, M	1994		235	Den Haag:Leiden	
Weber, J	1995		15	Metabolic Biochemist	HCAPLUS
White, A	1989	93A	455	Biochem Physiol A Ph	HCAPLUS
Williams, E	1994	266	R773	Am J Physiol, Regula	
Wittenberger, C	1968	13	131	Rev Roum Biol Zool	HCAPLUS
Wojcieszyn, J	1981	78	4407	Proc Natl Acad Sci U	HCAPLUS
Wolf, K	1963	25	135	Prog Fish-Cult	HCAPLUS
Wolfe, R	1987	252	E218	Am J Physiol, Endocr	
Wolfe, R	1992			Principles and Pract	
Wright, P	1989	147	169	J Exp Biol	HCAPLUS

L121 ANSWER 10 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:411407 HCAPLUS
DOCUMENT NUMBER: 122:210442
TITLE: Eicosanoid synthesis in cardiomyocytes: influence of hypoxia, reoxygenation, and polyunsaturated fatty acids
AUTHOR(S): Oudot, Fabien; Grynberg, Alain; Sergiel, Jean Pierre
CORPORATE SOURCE: Unite Nutrition Lipidique, Inst. Natl. Recherche Agronomique, Dijon, 21034, Fr.
SOURCE: American Journal of Physiology (**1995**), 268(1, Pt. 2), H308-H315
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis of eicosanoids was investigated in cultured rat ventricular myocytes. Under normoxia, the cardiomyocytes released 6-ketoprostaglandin F1α (6-keto-PGF1α) and prostaglandin (PG) E2 and smaller amts. of PGF2α and thromboxane B2. Hypoxia enhanced the production of PGE2 and PGF2α, whereas the synthesis of 6-keto-PGF1α was not affected. Conversely, posthypoxic reoxygenation greatly increased in synthesis of 6-keto-PGF1α, whereas the synthesis of PGF2α was not affected and that of PGE2 was reduced. The cardiomyocyte polyunsatd. fatty acid (PUFA) profile was altered by arachidonic acid or eicosapentaenoic acid and docosahexaenoic acid. Under normoxia, the eicosanoid production appeared to be roughly related to the cell phospholipid arachidonic acid content. Conversely, during posthypoxic reoxygenation, the production of eicosanoids was related to the cell phospholipid n-3 PUFA content, with the n-3 rich cells displaying a marked inhibition of the synthesis. This inhibition was mainly attributed to eicosapentaenoic acid and/or docosapentaenoic acid. Whether this inhibition occurs in vivo during postischemic reperfusion, it may contribute to the beneficial effect of n-3 PUFA on the heart.

IT **80558-45-8**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(effect of hypoxia, reoxygenation, and phospholipid polyunsatd. fatty acid composition on eicosanoid synthesis by heart cells)
RN 80558-45-8 HCAPLUS
CN Eicosatrienoic acid, (Z,Z,Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 506-30-9
CMF C20 H40 O2

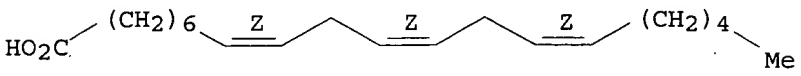
$HO_2C-(CH_2)_{18}-Me$

CC 13-2 (Mammalian Biochemistry)
Section cross-reference(s): 2
IT Heart
Hypoxia
(effect of hypoxia, reoxygenation, and polyunsatd. fatty acids on eicosanoid synthesis by heart cells)
IT 28984-77-2 31152-45-1 32839-18-2 32839-28-4 32839-30-8
32839-34-2 **80558-45-8** 81276-10-0
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(effect of hypoxia, reoxygenation, and phospholipid polyunsatd. fatty acid composition on eicosanoid synthesis by heart cells)

L121 ANSWER 11 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:226106 HCAPLUS
DOCUMENT NUMBER: 122:28229
TITLE: Energy status and free fatty acid patterns in tissues of common carp (Cyprinus carpio, L.) and rainbow trout (Oncorhynchus mykiss, L.) during severe oxygen restriction
AUTHOR(S): van Raaij, Marcel T. M.; Bakker, Erik; Nieveen, Maaike C.; Zirkzee, Hans; van den Thillart, Guido E. E. J. M.
CORPORATE SOURCE: Department Biology (Animal Physiology), State University Leiden, Leiden, 2300 RA, Neth.
SOURCE: Comparative Biochemistry and Physiology, A: Physiology (**1994**), 109A(3), 755-67
CODEN: CBPAB5; ISSN: 0300-9629
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Common carp and rainbow trout were exposed to a severe level of O restriction up to a near lethal value, to study the occurrence of tissue damage. Rainbow trout lost equilibrium at a PO2 of 3.2 kPa, whereas carp were able to survive 1.5 h of anoxia. In both species, the anaerobic metabolism was significantly activated and the energy status (phosphocreatine, ATP, and energy charge) was significantly depressed in brain, liver, and red and white muscle. No marked release of polyunsatd. fatty acids (PUFAs) to the free fatty acid (FFA) pool was observed, while membrane leakage was not increased as evidenced by plasma lactate dehydrogenase activity. These results indicate the absence of a marked hydrolysis of membrane lipids. Thus, even after a near lethal exposure to hypoxia or anoxia, no tissue damage occurs in fish liver and skeletal muscles. The changes of the FFA patterns in the skeletal muscles and liver of both species after O deprivation may be related to changes in desaturase activities, a reduction of lipolytic activity and PUFA metabolism
IT **1783-84-2 17046-59-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anoxia effect on fatty acids of brain and liver and muscle of fish)

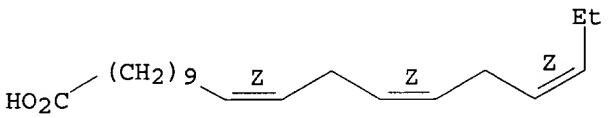
RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 17046-59-2 HCAPLUS
CN 11,14,17-Eicosatrienoic acid, (11Z,14Z,17Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



CC 12-6 (Nonmammalian Biochemistry)
IT Brain
Hypoxia
Liver
Oncorhynchus mykiss
(anoxia effect on fatty acids of brain and liver and muscle of fish)
IT 56-65-5, 5'-ATP, biological studies 57-10-3, Hexadecanoic acid, biological studies 57-11-4, C18:0, biological studies 58-64-0, 5'-ADP, biological studies 60-33-3, 9,12-Octadecadienoic acid (Z,Z)-, biological studies 61-19-8, 5'-AMP, biological studies 67-07-2, Phosphocreatine 86-01-1, 5'-GTP 112-80-1, 9-Octadecenoic acid (Z)-, biological studies 112-86-7 131-99-7, 5'-IMP 143-07-7, Dodecanoic acid, biological studies 373-49-9 463-40-1 506-30-9, Eicosanoic acid 506-32-1 506-37-6 544-63-8, Tetradecanoic acid, biological studies 544-64-9 1002-84-2, Pentadecanoic acid 1002-96-6 **1783-84-2** 2724-58-5 4669-02-7, Iso-C16:0 5070-03-1 5561-99-9 5598-38-9 6217-54-5 10417-94-4 17027-32-6 **17046-59-2** 24880-45-3 25182-74-5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anoxia effect on fatty acids of brain and liver and muscle of fish)

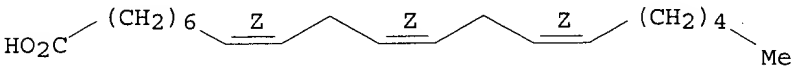
L121 ANSWER 12 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:130209 HCAPLUS
DOCUMENT NUMBER: 120:130209
TITLE: Lipid metabolism of goldfish, Carassius auratus (L.) during normoxia and anoxia. Indications for fatty acid chain elongation
AUTHOR(S): van Raaij, Marcel T. M.; Breukel, Bert Jan; van den Thillart, Guido E. E. J. M.; Addink, Albert D. F.
CORPORATE SOURCE: Dep. Biol., State Univ. Leiden, 2300 RA, Neth.
SOURCE: Comparative Biochemistry and Physiology, Part B: Biochemistry & Molecular Biology (**1994**), 107B(1), 75-84
CODEN: CBPBB8; ISSN: 0305-0491
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Goldfish acclimated to 20° and air-saturation levels of .apprx.80%, were subjected to 14 h anoxia. Fatty acid patterns of free fatty acids (FAA), triglycerides (TG), and phospholipids (PL) were determined in plasma, red

muscle, and peritoneal adipose tissue. After 14 h anoxia, the FFA content of both the red muscle and plasma were decreased by 50%, probably as a result of suppression of lipolytic activity. Anoxia induced major changes in the relative FFA pattern of both red muscle and plasma. Decreases were observed for 16:0, 16:1(n-7), 18:0, 18:1(n-9), and 18:2(n-6). Increases were observed for 20:0, 20:1(n-9), 20:3(n-6), and 22:1(n-11/n-9). Anoxia induced significant changes in the Σ(C18)/Σ(C20) and C18:1/C20:1 ratios. The fatty acid patterns of the PL and TG were not significantly changed by anoxia. Although the quant. importance could not be established, the present results are indicative for the presence of fatty acid chain elongation in anoxic goldfish starting preferentially with 18-carbon fatty acids.

IT **1783-84-2**, C20:3n-6
RL: BIOL (Biological study)
(of blood plasma and peritoneal adipose tissue and red muscle, of goldfish in hypoxia)

RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



CC 12-6 (Nonmammalian Biochemistry)

IT **Hypoxia**
(fatty acids of blood plasma and peritoneal adipose tissue and red muscle of goldfish in)

IT 57-10-3, C16:0, biological studies 57-11-4, C18:0, biological studies 60-33-3, C18:2n-6, biological studies 112-80-1, C18:1n-9, biological studies 112-86-7, C22:1n-9 143-07-7, C12:0, biological studies 334-48-5, C10:0 373-49-9, C16:1n-7 463-40-1, C18:3n-3 506-17-2, C18:1n-7 506-26-3, C18:3n-6 506-30-9, C20:0 506-32-1, C20:4n-6 506-37-6, C24:1n-9 544-63-8, C14:0, biological studies 544-64-9, C14:1n-5 638-53-9, C13:0 1002-84-2, C15:0 1002-96-6, C22:1n-11 **1783-84-2**, C20:3n-6 1903-03-3, C15:1n-6 2724-57-4, Iso C14:0 2724-58-5, Iso C18:0 4669-02-7, Iso C16:0 5502-94-3, Anteiso C15:0 5561-99-9, C20:1n-9 5598-38-9, C20:2n-6 6217-54-5, C22:6n-3 7416-57-1, Anteiso C13:0 10417-94-4, C20:5n-3 17027-32-6, C18:2n-3 17735-95-4, C20:1n-6 24880-40-8, C20:4n-3 24880-45-3, C22:5n-3 25182-74-5, C22:5n-6 28039-98-7, C14:1 28290-73-5, C16:2n-6 29564-66-7, C22:2 32839-24-0, C16:3 32839-33-1, C22:3 125535-14-0, C20:2n-3
RL: BIOL (Biological study)
(of blood plasma and peritoneal adipose tissue and red muscle, of goldfish in hypoxia)

L121 ANSWER 13 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:551363 HCAPLUS
DOCUMENT NUMBER: 111:151363
TITLE: Mechanism of hypoxic injury to pulmonary artery endothelial cell plasma membranes
AUTHOR(S): Block, Edward R.; Patel, Jawaharlal M.; Edwards, Deborah
CORPORATE SOURCE: Res. Serv., V.A. Med. Cent., Gainesville, FL, 32602, USA
SOURCE: American Journal of Physiology (**1989**), 257(2, Pt. 1), C223-C231

CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Monolayer cultures of pulmonary artery endothelial cells or plasma membranes derived from these cells were exposed to hypoxic (0 and 5% O2) and normoxic (20% O2; control) conditions and the cellular contents of malondialdehyde and conjugated dienes, plasma membrane fluidity and lipid composition, and plasma membrane-dependent transport of 5-HT were measured. Hypoxia caused significant increases in malondialdehyde and conjugated dienes, in fluidity, and in 5-HT transport. Hypoxia also caused a decrease in plasma membrane total phospholipids and a marked increase in plasma membrane free fatty acids that appeared to be due to release of fatty acids from the plasma membrane phospholipids. The increases in fluidity and 5-HT transport and the alterations in fatty acids were reversible after return to control conditions. Thus, hypoxia alters the phys. state, lipid composition, and function of endothelial cell plasma membranes by a combination of stimulation of membrane lipid peroxidn. and accelerated degradation of membrane phospholipids, the latter probably secondary to activation of membrane phospholipases.
IT **80558-45-8**
RL: BIOL (Biological study)
(of pulmonary artery endothelial cell membrane, hypoxia effect on)
RN 80558-45-8 HCAPLUS
CN Eicosatrienoic acid, (Z,Z,Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 506-30-9
CMF C20 H40 O2

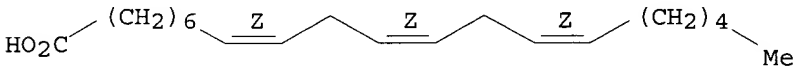
$HO_2C-(CH_2)_{18}-Me$

CC 14-5 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 13
IT **Hypoxia**
(pulmonary artery endothelial cell membrane injury from, lipid peroxidn. and phospholipid degradation in)
IT 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 506-30-9, Eicosanoic acid 544-63-8, Tetradecanoic acid, biological studies 557-59-5, Tetracosanoic acid 27104-13-8 27213-43-0 28039-98-7 28039-99-8 28929-01-3 28933-89-3 28984-77-2 31152-45-1 31152-46-2 32839-18-2 32839-28-4 32839-30-8 32839-34-2 **80558-45-8**
RL: BIOL (Biological study)
(of pulmonary artery endothelial cell membrane, hypoxia effect on)

L121 ANSWER 14 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:571421 HCAPLUS
DOCUMENT NUMBER: 111:171421
TITLE: Effects of various oxygen concentrations on antioxidant enzymes and the quantity of tissue phospholipid fatty acids in the carp
AUTHOR(S): Radi, A. A. R.; Matkovics, B.; Csengeri, I.
CORPORATE SOURCE: Biol. Isot. Lab., Jozsef Attila Univ., Szeged, Hung.
SOURCE: Acta Biologica Hungarica (**1988**), 39(1), 109-19, 2 plates
CODEN: ABHUE6; ISSN: 0236-5383
DOCUMENT TYPE: Journal

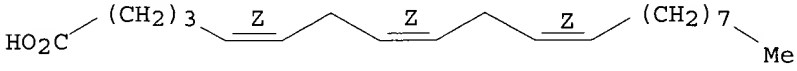
LANGUAGE: English
AB Analyses were made of the phospholipid fatty acids and the antioxidant enzymes in the carp (Cyprinus carpio morpha) at 3 different O concns., corresponding to hyperoxia, hypoxia, and anoxia. Variations of the O concentration influenced the quantities of phospholipid fatty acids, as well as the antioxidant enzyme activities. In hyperoxia and hypoxia the amount of polyunsatd. fatty acids in carp liver was higher than in anoxia, but in other tissues there was no significant differences. As to the antioxidant enzyme system, the glutathione peroxidase activity and the lipid peroxidn. value increased significantly with decreases in the O concentration, whereas the total superoxide dismutase activity decreased on lowering of the O level.
IT **1783-84-2 20590-32-3**
RL: BIOL (Biological study)
(of phospholipids, of gill and liver and muscle of carp, oxygen concentration effect on)
RN 1783-84-2 HCAPLUS
CN 8,11,14-Eicosatrienoic acid, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 20590-32-3 HCAPLUS
CN 5,8,11-Eicosatrienoic acid, (5Z,8Z,11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



CC 12-6 (Nonmammalian Biochemistry)
Section cross-reference(s): 4
IT Hyperoxia
Hypoxia
(antioxidant enzymes and fatty acids of phospholipids of carp in)
IT 57-10-3, Hexadecanoic acid, biological studies 57-11-4, C18:0, biological studies 60-33-3, 9,12-Octadecadienoic acid (Z,Z)-, biological studies 112-80-1, 9-Octadecenoic acid (Z)-, biological studies 373-49-9 463-40-1 506-26-3 506-32-1 544-63-8, Tetradecanoic acid, biological studies 1002-84-2, Pentadecanoic acid **1783-84-2** 5561-99-9 5598-38-9 6217-54-5 10417-94-4 **20590-32-3** 24880-40-8 24880-45-3 25182-74-5 28874-58-0 80782-80-5
RL: BIOL (Biological study)
(of phospholipids, of gill and liver and muscle of carp, oxygen concentration effect on)

L121 ANSWER 15 OF 45 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:21861 HCAPLUS
DOCUMENT NUMBER: 110:21861
TITLE: Effect of moderate hypoxia on content and pattern of free fatty acids in cerebral white matter
AUTHOR(S): Wender, Mieczyslaw; Adamczewska-Goncerzewicz, Zofia;

Zorawski, Andrzej; Sroczynski, Eugeniusz; Grochowalska, Alina
CORPORATE SOURCE: Dep. Neurol., Sch. Med., Poznan, Pol.
SOURCE: Neuropatologia Polska (**1988**), 26(1), 39-47
CODEN: NUPOBT; ISSN: 0028-3894
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rats were subjected to mild hypoxia (whole-body) and their cerebral white matter was analyzed for free fatty acids 4 min, 4 h, 24 h, 14 days, and 2 mo after the hypoxic episode. Those fatty acid profiles are presented. In general, fatty acids increased after hypoxia, and arachidonic acid and nervonic acid showed the most striking alterations.
IT **80558-45-8**
RL: BIOL (Biological study)
(of brain white matter, hypoxia effect on)
RN 80558-45-8 HCAPLUS
CN Eicosatrienoic acid, (Z,Z,Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 506-30-9
CMF C20 H40 O2

$HO_2C-(CH_2)_{18}-Me$

CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 13
IT **Hypoxia**
(fatty acids of brain white matter response to)
IT 57-10-3, biological studies 57-11-4, C18:0, biological studies 112-80-1, biological studies 143-07-7, biological studies 506-12-7 506-30-9 506-32-1 544-63-8, biological studies 557-59-5 1002-84-2 27213-43-0 28039-99-8 28933-89-3 28984-77-2 31152-46-2 32839-28-4 32839-30-8 **80558-45-8**
RL: BIOL (Biological study)
(of brain white matter, hypoxia effect on)

=> d ibib abs 16-24

L121 ANSWER 16 OF 45 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 96199323 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8967376
TITLE: Inhibition of cytochrome P-450 attenuates **hypoxemia** of acute lung injury in dogs.
AUTHOR: Stephenson A H; Sprague R S; Weintraub N L; McMurdo L; Lonigro A J
CORPORATE SOURCE: Department of Pharmacological and Physiological Science, Saint Louis University, School of Medicine, Missouri 63104, USA.
CONTRACT NUMBER: HL-30572 (NHLBI)
HL-52675 (NHLBI)
SOURCE: American journal of physiology, **(1996 Apr)** 270 (4 Pt 2) H1355-62.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961204

AB The intravenous administration of ethchlorvynol (ECV), in dogs, resulted in an acute lung injury (ALI) characterized by a 200 +/- 80% increase in venous admixture and a 142 +/- 30% increase in extravascular lung water (EVLW). Pretreatment with the cytochrome P-450 inhibitor 8-methoxypsoralen prevented the ECV-induced increase in venous admixture but not the increased EVLW. These findings parallel those reported for cyclooxygenase inhibition in ECV-induced ALI and suggest that an arachidonic acid (AA) metabolite of pulmonary cytochrome P-450 activity may mediate the increase in venous admixture of ALI. We demonstrate that canine pulmonary microsomes metabolize [1-(14)C]AA to a variety of products, including the cytochrome P-450 metabolites 5,6-, 8,9-, 11,12-, and **14,15-epoxyeicosatrienoic acid** (EET). In prostaglandin F2 alpha-contracted, isolated pulmonary venous rings, 5,6-EET induced relaxation in a concentration-dependent manner. This action of 5,6-EET was prevented by indomethacin (10(-5) M). These results suggest that may serve as the cyclooxygenase-dependent endogenous pulmonary vasodilator responsible for the increase in venous admixture of ECV-induced ALI.

L121 ANSWER 17 OF 45 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 94267348 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8207335
TITLE: Effect of metabolic inhibitors on arachidonic acid metabolism in the corneal epithelium: evidence for cytochrome P450-mediated reactions.
AUTHOR: Stoltz R A; Conners M S; Dunn M W; Schwartzman M L
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla.
CONTRACT NUMBER: EY06513 (NEI)
SOURCE: Journal of ocular pharmacology, **(1994 Spring)** 10 (1) 307-17.
Journal code: 8511297. ISSN: 8756-3320.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940721
Last Updated on STN: 19940721
Entered Medline: 19940713

AB The corneal epithelium of several species, has the capacity to metabolize arachidonic acid (arachidonic acid) via an NADPH-dependent cytochrome P450 mechanism. The major metabolites are 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) and 12-hydroxy-5,8,14-eicosatrienoic acid (12-HETrE), both of which exist in stereoisomeric configurations. However, the R enantiomers are predominantly produced by this enzyme system and exhibit potent biological activities. 12(R)-HETE inhibits Na-K-ATPase, increases corneal thickness and reduces intraocular pressure. 12(R)-HETrE causes vasodilation, neutrophil chemoattraction and angiogenesis. The formation of these metabolites is unaffected by cyclooxygenase and lipoxygenase inhibitors (indomethacin, diclofenac and BW755C) but inhibited by cytochrome P450 enzyme inhibitors such as carbon monoxide, SKF-525A and clotrimazole. The capacity of the normal corneal epithelium to metabolize arachidonic acid via cytochrome P450 is very low although under certain conditions this enzymatic pathway may become

greatly induced. Corneal epithelial **hypoxia** in response to contact lens wear results in the time-dependent formation of NADPH-cytochrome P450-dependent arachidonate metabolites, 12(R)-HETE and 12(R)-HETrE. Under this condition, metabolite production correlates strongly with the in situ inflammatory response and inhibition of their formation significantly attenuates inflammation. It is evident that the cytochrome P450 arachidonate metabolites should be added to the realm of cyclooxygenase and lipoxygenase-derived eicosanoids as possible inflammatory mediators. Therefore, studies to evaluate eicosanoid involvement in inflammation should examine inhibitors of this pathway in addition to the classically studied non-steroidal antiinflammatory drugs (NSAIDs).

L121 ANSWER 18 OF 45 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 92155889 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1740358
TITLE: Induction of corneal epithelial cytochrome P-450 arachidonate metabolism by contact lens wear.
AUTHOR: Davis K L; Conners M S; Dunn M W; Schwartzman M L
CORPORATE SOURCE: Department of Pharmacology, New York Medical College, Valhalla.
CONTRACT NUMBER: EY06513 (NEI)
SOURCE: Investigative ophthalmology & visual science, **(1992 Feb)** 33 (2) 291-7.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920410
Last Updated on STN: 19970203
Entered Medline: 19920323

AB Two biologically active cytochrome P-450 arachidonate metabolites previously were characterized: 12(R)-hydroxy-5,8,10,14-eicosatetraenoic acid (12(R)-HETE) and 12(R)-hydroxy-5,8,14-eicosatrienoic acid (12(R)-DH-HETE), which are endogenously formed in the corneal epithelium. The functional activity of these novel metabolites mimics changes observed in hypoxic corneas. Therefore, the effect of hypoxic stress was examined on metabolite formation in rabbits fitted with polymethylmethacrylate contact lenses. Although applied lenses fit tightly to the rabbit cornea, mechanical irritation also may contribute to the ocular response. Contact lens-induced hypoxic stress stimulated endogenous formation of both 12(R)-HETE (a sodium, potassium adenosine triphosphatase inhibitor) and 12(R)-DH-HETE (a vasodilatory, chemotactic, and angiogenic factor) in a time-dependent manner. After 4 hr of contact lens wear, a 21-fold increase in endogenous 12(R)-HETE formation concomitant with an increase in corneal thickness was observed. After prolonged contact lens wear (144 hr), a 23-fold increase in endogenous 12(R)-DH-HETE formation was found, corresponding with the appearance of a marked conjunctival inflammation characterized by corneal neovascularization. The increased formation of these compounds was associated with time-dependent changes in corneal endothelial morphology. The ability of 12(R)-HETE and 12(R)-DH-HETE to mediate the clinical signs of corneal **hypoxia** suggest these metabolites may be potential mediators of contact lens complications that followed conditions of hypoxic stress and possibly mechanical irritation in this model.

L121 ANSWER 19 OF 45 MEDLINE on STN
ACCESSION NUMBER: 1998368910 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9701713
TITLE: Characterization of endothelium- dependent relaxation in guinea pig basilar artery - effect of **hypoxia** and role of cytochrome P450 mono-oxygenase.
AUTHOR: Petersson J; Zygmunt P M; Jonsson P; Hogestatt E D
CORPORATE SOURCE: Department of Clinical Pharmacology, Institute of Laboratory Medicine, Lund University Hospital, Lund, Sweden.
SOURCE: Journal of vascular research, **(1998 Jul-Aug)** 35 (4) 285-94.
Journal code: 9206092. ISSN: 1018-1172.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 19981006
Entered Medline: 19980918

AB In the guinea pig basilar artery, acetylcholine and the calcium ionophore A23187 induced endothelium-dependent relaxations, which were not significantly affected by the nitric oxide (NO) synthase inhibitor Nomega-nitro-L-arginine (L-NOARG; 0.3 mM) or the guanylate cyclase inhibitor ODQ (1H-[1,2,4]oxadiazolo[4,3-a]quinoxaline-1-one; 1-10 microM), or by these inhibitors combined. However, acetylcholine (10 microM) and A23187 (3 microM) each significantly increased the tissue level of cGMP in the absence but not in the presence of L-NOARG, suggesting that NO is released from the vascular endothelium in this blood vessel. Treatment with the potassium (K) channel inhibitors charybdotoxin (0.1 microM) plus apamin (0.1 microM), a toxin mixture previously shown to inhibit relaxations mediated by endothelium-derived hyperpolarizing factor (EDHF) in this artery, had no effect on the A23187-induced relaxation but slightly inhibited the response to acetylcholine (Emax was reduced by 24%). When the action of EDHF was prevented by these K channel inhibitors, the remaining relaxation was abolished by either ODQ (1 microM) or L-NOARG (0.3 mM), indicating that NO, apart from EDHF, contributes to the endothelium-dependent relaxations. Furthermore, ODQ (10 microM) abolished the relaxation induced by the NO donor S-nitroso-N-acetylpenicillamine. Thus, activation of soluble guanylate cyclase seems to be the only mechanism through which NO causes relaxation in this artery. When vessels were exposed to grave **hypoxia** (pO2 = 6 mm Hg), the NO-mediated relaxation (induced by acetylcholine in the presence of charybdotoxin plus apamin) disappeared. In contrast, EDHF-mediated responses (elicited by acetylcholine in the presence of L-NOARG) were only marginally affected by **hypoxia** (Emax was reduced by 16%). 17-Octadecynoic acid (50 microM) and 5,8,11,14-eicosatetraynoic acid (10 microM), inhibitors of cytochrome P450-dependent oxidation of arachidonic acid, failed to inhibit the acetylcholine-induced relaxation in the presence of L-NOARG. The cytochrome P450-dependent arachidonic acid metabolite 11,12-epoxyecosatrienoic acid (0.3-3.0 microM) had no relaxant effect per se. In conclusion, EDHF and NO are both mediators of endothelium-dependent relaxations in the guinea pig basilar artery. However, during grave **hypoxia**, EDHF alone mediates acetylcholine-induced relaxation. The results further suggest that EDHF is not a metabolite of arachidonic acid formed by cytochrome P450 mono-oxygenase or generated by another oxygen-dependent enzyme in this artery.

L121 ANSWER 20 OF 45 MEDLINE on STN
ACCESSION NUMBER: 94162538 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8117956
TITLE: [A comparison of the effects of 5-hydroxyeicosatetraenoic acid and hepoxilin A3 on the plasticity of the snail neuronal cholinoreceptors].
Sravnenie effektov 5-gidroksieikozatetraenovoi kisloty i gepoksilina A3 na plastichnost' kholinoretseptorov neironov vinogradnoi ulitki.
AUTHOR: Pivovarov A S; Demin P M; Miagkova G I
SOURCE: Biulleten' eksperimental'noi biologii i meditsiny, **(1993 Oct)** 116 (10) 378-81.
Journal code: 0370627. ISSN: 0365-9615.
PUB. COUNTRY: RUSSIA: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19940412
Entered Medline: 19940407

AB The effects of two acyclic derivatives of arachidonic acid which are formed under the action of 5- and 12-lipoxygenases 5(S)-hydroxy-(6,8Z,11Z,14Z)-eicosatetraenoic acid (5-HETE) and (8R/S)-hydroxy-(11S,12S)-epoxy-5Z,9E,14Z-eicosatrienoi c acid (hepoxilin A3) on extinction of inward current evoked by local acetylcholine (ACh-current) application on soma of Helix lucorum RPa3 and LPa3 neurons were studied by the double-electrode voltage clamp technique. It was shown an increase in ACh-current extinction by 5-HETE. Hepoxilin A3 did not influence cholinoreceptor plasticity. The present results confirm earlier assumptions concerning the regulation of cholinoreceptor plasticity by acyclic eicosanoids which were formed from arachidonic acid under the influence of 5-**lipoxygenase** and the **lack** of 12-**lipoxygenase** metabolites in this regulation.

L121 ANSWER 21 OF 45 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 4
ACCESSION NUMBER: 1998330364 EMBASE
TITLE: Dietary juniper berry oil minimizes hepatic reperfusion injury in the rat.
AUTHOR: Jones S.M.; Zhong Z.; Enomoto N.; Schemmer P.; Thurman R.G.
CORPORATE SOURCE: Dr. R.G. Thurman, Lab. of Hepatobiology and Toxicology, Department of Pharmacology, University of North Carolina, Chapel Hill, NC 27599-7365, United States
SOURCE: Hepatology, (1998) 28/4 I (1042-1050).
Refs: 38
ISSN: 0270-9139 CODEN: HPTLD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Juniper berry oil is rich in 5,11,14-**eicosatrienoic** acid, a polyunsaturated fatty acid similar to one found in fish oil, yet less prone to peroxidation. Dietary fish oil treatment has been shown to effectively reduce reperfusion injury; therefore, the effects of a diet containing juniper berry oil on hepatic reperfusion injury in a low-flow, reflow reperfusion model were investigated in the rat. Rats were fed semisynthetic diets containing either juniper berry oil, fish oil, or corn oil for 14 to 16 days. Daily food consumption averaged around 20 g/d in both the control and treatment groups; average daily weight gain was

around 4 g per 100 g rat weight in all three groups studied, and there were no significant differences in these parameters. Livers were initially perfused at low-flow rates to induce pericentral **hypoxia** followed by a 40-minute reperfusion period. Peak lactate dehydrogenase (LDH) release during reflow averaged 44 U/g/h in the corn oil group and 32 U/g/h in the fish oil group, but was only 21 U/g/h as a result of juniper berry oil treatment. Malondialdehyde (MDA), an end-product of lipid peroxidation, reached a maximum value of 62 nmol/g/h in the corn oil group, but only reached 43 nmol/g/h and 34 nmol/g/h in the fish oil and juniper berry oil groups, respectively. Both juniper berry oil and fish oil treatment improved rates of bile flow from 25 μL/g/h (corn oil) to 36 and 38 μL/g/h, respectively. Importantly, juniper berry oil reduced cell death in pericentral regions of the liver lobule by 75%. Trypan blue distribution time, an indicator of the hepatic microcirculation, was reduced by approximately 25% with fish off and over 50% by juniper berry oil diets compared with corn off controls. The rates of entry of fluorescein-dextran, a dye confined to the vascular space, were increased 1.8- and 2.6-fold, and rates of outflow were increased 4.4- and 4.3-fold by fish oil and juniper berry oil, respectively, also reflecting improved microcirculation. Juniper berry oil also blunted increases in intracellular calcium and release of prostaglandin E2 (PGE2) by cultured Kupffer cells stimulated by endotoxin. These results are consistent with the hypothesis that feeding a diet containing juniper berry oil reduces reperfusion injury by inhibiting activation of Kupffer cells, thus reducing vasoactive eicosanoid release and improving the hepatic microcirculation in livers undergoing oxidant stress.

L121 ANSWER 22 OF 45 EMBASE
on STN DUPLICATE 10

ACCESSION NUMBER: 77144531 EMBASE
DOCUMENT NUMBER: 1977144531
TITLE: Comparative studies on fatty acid synthesis in atherosclerotic and **hypoxic** human aorta.
AUTHOR: Filipovic I.; Rutemoeller M.
CORPORATE SOURCE: Inst. Physiol. Chem., Univ. Munster, Germany
SOURCE: Atherosclerosis, (1976) 24/3 (457-469).
CODEN: ATHSBL
DOCUMENT TYPE: Journal
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
023 Nuclear Medicine
029 Clinical Biochemistry
LANGUAGE: English

AB The oxygen and glucose uptake, lactate formation, ATP/ADP and NADH/NAD ratios and incorporation of [14C]acetate and [14C]linolenic acid into lipids of early fatty streaks and more advanced complicated atherosclerotic lesions of human aorta were determined during aerobic and **hypoxic** incubation. Compared with grossly normal appearing sections of the aorta in intima and media preparations of early fatty streaks the oxygen uptake was increased while that in further developed atheroma was slightly diminished. Under aerobic incubation conditions the metabolic state of fatty streaks and atheroma was characterized by increased lactate formation, NADH/NAD ratio and incorporation of [14C]acetate and [14C]linolenic acid into the lipids, but by a lowered ATP/ADP ratio. More pronounced changes in these metabolic parameters were observed when the aortic tissue segments were incubated under **hypoxic** conditions. The analysis by argentation TLC of fatty acid methylesters derived from total lipids of aerobically incubated fatty streaks revealed an increased incorporation of [14C]acetate into the highly unsaturated long chain fatty acids. In developed atherosclerotic lesions and in **hypoxia** the incorporation of radioacetate into

the polyunsaturated fatty acids and the formation of 20:4 fatty acid from [14C]linolenic acid were, in contrast to the above finding, decreased while the synthesis of **eicosatrienoic** acid was increased. This finding suggests a block in the desaturation step of linoleic into 20:4 fatty acid in further developed atheroma and in **hypoxia.** In aerobically incubated atherosclerotic lesions and in **hypoxia** in the palmitic acid was synthesized mainly by chain elongation while in grossly normal areas of the aorta at least part of this acid was synthesized de novo.

L121 ANSWER 23 OF 45 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999100896 EMBASE
TITLE: **Hypoxia** stimulates the synthesis of cytochrome P450-derived inflammatory eicosanoids in rabbit corneal epithelium.
AUTHOR: Vafeas C.; Mieyal P.A.; Urbano F.; Falck J.R.; Chauhan K.; Berman M.; Schwartzman M.L.
CORPORATE SOURCE: Dr. M.L. Schwartzman, Department of Pharmacology, New York Medical College, Valhalla, NY 10595, United States
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1998) 286/3 (903-910).
Refs: 43
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The corneal epithelium metabolizes arachidonic acid by a cytochrome P450-(CYP) mediated pathway to 12(R)hydroxy-5,8,10,14-**eicosatrienoic** acid [12(R)-HETE] and 12(R)hydroxy-5,8,14-**eicosatrienoic** acid [12(R)-HETrE]. Both metabolites possess potent inflammatory properties with 12(R)-HETrE being a powerful angiogenic factor and assume the role of inflammatory mediators in **hypoxia**- and chemical-induced injury in the cornea, in vivo. We developed an in vitro model of corneal organ culture to characterize the biochemical and molecular events involved in the increased synthesis of these metabolites. These cultured corneas exhibit epithelial cytochrome P450 CYP-dependent 12(R)-HETE and 12(R)-HETrE synthesis as indicated by chiral analysis and by the ability of CYP enzyme inhibitors to repress their synthesis. **Hypoxia** greatly and selectively stimulated the synthesis of 12(R)-HETE (7-fold over control normoxic conditions) and 12(R)-HETrE. The bacterial endotoxin, lipopolysaccharide, also increased the synthesis of these eicosanoids, substantiating the notion that this activity may function as an inflammatory pathway. These metabolites were detected in the culture medium by gas chromatography/mass spectroscopy (GC/MS) analysis and their levels significantly increased in **hypoxia** -treated corneas, further indicating their endogenous formation in response to injury. This in vitro model provides an excellent preparation for studying factors regulating the synthesis of these inflammatory eicosanoids and for isolating, identifying and characterizing the CYP protein responsible for their synthesis.

L121 ANSWER 24 OF 45 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1998275424 EMBASE
TITLE: **5,6-Epoxyeicosatrienoic acid** reduces increases in pulmonary vascular

resistance in the dog.
AUTHOR: Stephenson A.H.; Sprague R.S.; Lonigro A.J.
CORPORATE SOURCE: A.H. Stephenson, Clinical Pharmacology, St. Louis Univ. School of Medicine, 1402 S. Grand Blvd., St. Louis, MO 63104, United States
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (1998) 275/1 44-1 (H100-H109).
Refs: 47
ISSN: 0363-6135 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We recently reported that canine pulmonary microsomes metabolize arachidonic acid to all four regioisomeric **epoxyeicosatrienoic acids** (EET). 5,6-EET dilates blood vessels in several nonpulmonary vascular beds, often in a cyclooxygenase-dependent manner. The present study was designed to determine whether 5,6-EET can decrease pulmonary vascular resistance (PVR) in the intact pulmonary circulation. In isolated canine lungs perfused with physiological salt solution, a constant infusion of U-46619 (3.28 + 0.99 nmol/min) increased PVR 62.1 ± 4.5%. Administration of 5,6-EET (10-5 M) into the perfusate reduced the U-46619-mediated increase in PVR by 23.6 ± 6.1%. These effects of U-46619 and 5,6-EET were limited to changes in resistance solely in the pulmonary venous segment. In contrast, venous as well as arterial segmental resistances were increased in 5-hydroxytryptamine (5-HT)-treated lungs. However, in the latter instance, 5,6-EET reduced arterial but not venous segmental resistance. 5,6-EET increased pulmonary PGI2 synthesis from 70.5 ± 18.4 to 675.9 ± 125.4 ng/min. In the presence of indomethacin (10-4 M), 5,6-EET did not increase PGI2 synthesis nor did it decrease U-46619- or 5-HT-mediated increases in PVR. In canine intrapulmonary vessels, 5,6-EET decreased active tension in veins contracted with U-46619. 5,6-EET decreased active tension in arteries but not veins contracted with 5-HT, consistent with results in the perfused lungs. These results demonstrate that 5,6-EET is a vasodilator in the intact pulmonary circulation. Its dilator activity depends on the constrictor agent present, the segmental resistance, and cyclooxygenase activity.

=> d ibib abs hitstr 25-26

L121 ANSWER 25 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2002:149199 USPATFULL
TITLE: Use of epoxyeicosatrienoic acids in the treatment of cerebrovascular conditions
INVENTOR(S): Liao, James K., Weston, MA, UNITED STATES
Moskowitz, Michael A., Belmont, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002077355	A1	20020620	
APPLICATION INFO.:	US 2001-870425	A1	20010530	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-207978P	20000530	(60)

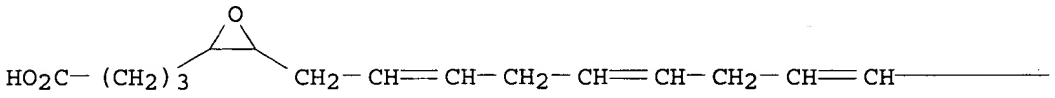
DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOLF GREENFIELD & SACKS, PC, FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 726
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the use of epoxyeicosatrienoic acids and/or inducers of cytochrome P-450 epoxygenase activity to reduce brain injury in a subject with a cerebrovascular condition, including stroke.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **81246-84-6 81246-85-7 81276-02-0**
81276-03-1 97717-69-6, Epoxyeicosatrienoic acid
(use of epoxyeicosatrienoic acids and cytochrome P 450 arachidonic acid epoxygenase inducers in treatment of brain injury from a cerebrovascular condition)
RN 81246-84-6 USPATFULL
CN Oxiranebutanoic acid, 3-(2,5,8-tetradecatrienyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

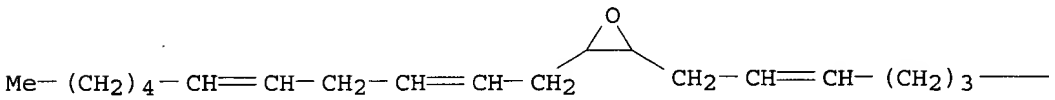


PAGE 1-B

— $(CH_2)_4$ — Me

RN 81246-85-7 USPATFULL
CN 5-Heptenoic acid, 7-[3-(2,5-undecadienyl)oxiranyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

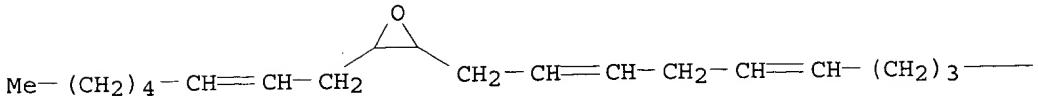


PAGE 1-B

— CO_2H

RN 81276-02-0 USPATFULL
CN 5,8-Decadienoic acid, 10-[3-(2-octenyl)oxiranyl]- (9CI) (CA INDEX NAME)

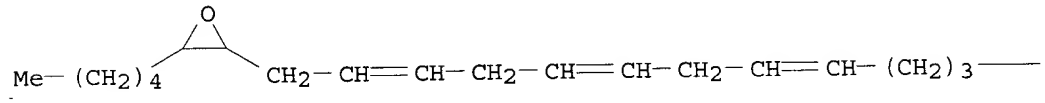
PAGE 1-A



PAGE 1-B

RN 81276-03-1 USPATFULL
CN 5,8,11-Tridecatrienoic acid, 13-(3-pentyloxiranyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

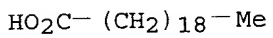


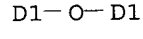
PAGE 1-B

RN 97717-69-6 USPATFULL
CN Eicosatrienoic acid, epoxy- (9CI) (CA INDEX NAME)

CM 1

CRN 97717-68-5
CMF C20 H38 O3
CCI IDS
CDES 8:ID





L121 ANSWER 26 OF 45 USPATFULL on STN
ACCESSION NUMBER: 1998:138733 USPATFULL
TITLE: Cytochrome P450 arachidonic acid epoxygenase genetic mutation associated with hypertension
INVENTOR(S): Capdevila, Jorge H., Nashville, TN, United States
Makita, Keiko, Nashville, TN, United States
Karara, Armando, Buenos Aires, Argentina

PATENT ASSIGNEE(S): Vanderbilt University, Nashville, TN, United States (U.S. corporation)

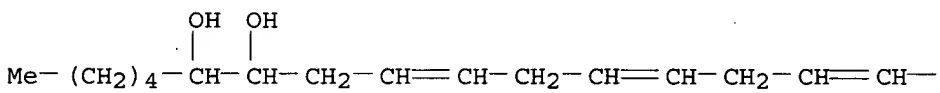
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5834293		19981110
APPLICATION INFO.:	US 1994-314601		19940928 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Chambers, Jasemin C.
ASSISTANT EXAMINER: Hauda, Karen M.
LEGAL REPRESENTATIVE: Needle & Rosenberg, P.C.
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 1371
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides an isolated nucleic acid encoding the rat P450 2C11 arachidonic acid epoxygenase, or a human homologue thereof, having a mutation associated with salt induced hypertension. Also provided is an isolated cell line expressing the epoxygenase encoded by the mutated nucleic acid, and a non-human transgenic animal having a germ line insertion of the mutated nucleic acid. Also provided is a method of screening a compound for efficacy in treating salt induced hypertension comprising administering the compound to such a non-human transgenic animal, and detecting an improvement in the animal's hypertension. The invention also provides a method of screening a human subject for a genetic predisposition to salt induced hypertension comprising detecting a mutation in a human homologue of a rat P450 2C11 arachidonic acid epoxygenase gene which affects normal epoxygenase activity. Also provided is a method of treating salt induced hypertension in a human subject associated with a genetic mutation in a human homologue of the rat P450 2C11 arachidonic acid epoxygenase gene, comprising administering to the subject a functional metabolite, or analogue thereof, produced by the human homologue of the rat P450 2C11 arachidonic acid epoxygenase. Also provided is an isolated mutated rat P450 2C11 arachidonic acid epoxygenase, or a human homologue thereof, having a mutation associated with salt induced hypertension.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **79551-81-8 79551-82-9 81246-84-6**
81246-85-7 81276-02-0 81276-03-1
81920-20-9 81943-03-5
(anti-hypertensive metabolite; cloning of cDNA for rat cytochrome P 450 arachidonic acid epoxygenase mutant associated with hypertension)
RN 79551-81-8 USPATFULL
CN 5,8,11-Eicosatrienoic acid, 14,15-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

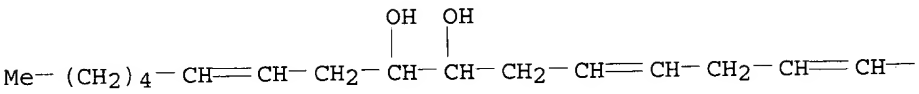


PAGE 1-B

— $(CH_2)_3$ — CO_2H

RN 79551-82-9 USPATFULL
CN 5,8,14-Eicosatrienoic acid, 11,12-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

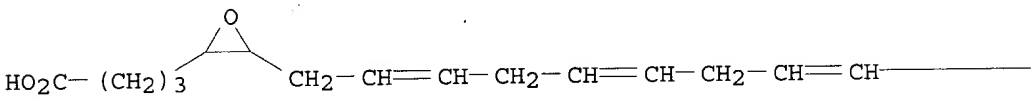


PAGE 1-B

— $(CH_2)_3$ — CO_2H

RN 81246-84-6 USPATFULL
CN Oxiranebutanoic acid, 3-(2,5,8-tetradecatrienyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

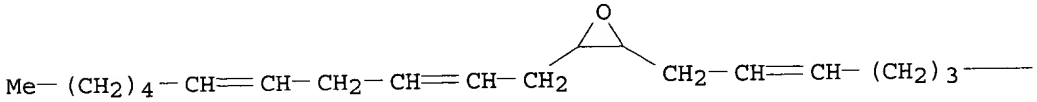


PAGE 1-B

— $(CH_2)_4$ — Me

RN 81246-85-7 USPATFULL
CN 5-Heptenoic acid, 7-[3-(2,5-undecadienyl)oxiranyl]- (9CI) (CA INDEX NAME)

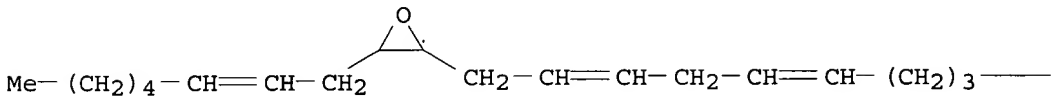
PAGE 1-A



PAGE 1-B

RN 81276-02-0 USPATFULL
CN 5,8-Decadienoic acid, 10-[3-(2-octenyl)oxiranyl]- (9CI) (CA INDEX NAME)

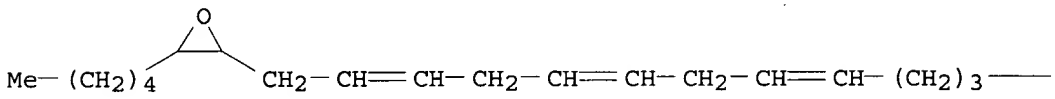
PAGE 1-A



PAGE 1-B

RN 81276-03-1 USPATFULL
CN 5,8,11-Tridecatrienoic acid, 13-(3-pentyloxiranyl)- (9CI) (CA INDEX NAME)

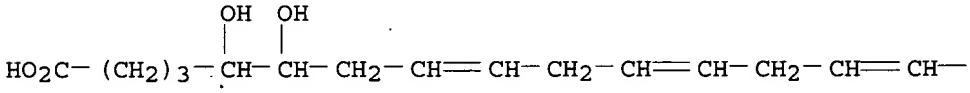
PAGE 1-A



PAGE 1-B

RN 81920-20-9 USPATFULL
CN 8,11,14-Eicosatrienoic acid, 5,6-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

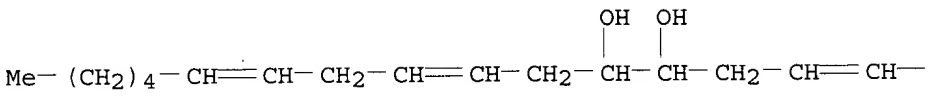


PAGE 1-B

— $(CH_2)_4$ — Me

RN 81943-03-5 USPATFULL
CN 5,11,14-Eicosatrienoic acid, 8,9-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

— $(CH_2)_3$ — CO_2H

=> d ibib abs 27

L121 ANSWER 27 OF 45 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:179098 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA13917259174P
TITLE: Cytochrome P-450 epoxygenase products contribute to attenuated vasoconstriction after chronic **hypoxia**
AUTHOR(S): Earley, Scott; Pastuszyn, Andrzej; Walker, Benjimen R.
CORPORATE SOURCE: Vascular Physiology Group, Departments of Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, NM, 87131, USA.
SOURCE: American Journal of Physiology, (2003) Vol. 285, No. 1, Pt. 2, pp. H127-H136.
CODEN: AJPHAP. ISSN: 0002-9513.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2003:555151
LANGUAGE: English
ENTRY DATE: Entered STN: 20030722
Last Updated on STN: 20040914

AB The systemic vasculature exhibits attenuated vasoconstriction following chronic **hypoxia** (CH) that is associated with endothelium-dependent vascular smooth muscle (VSM) cell hyperpolarization. We hypothesized that increased production of arachidonic acid metabolites such as the cyclooxygenase product prostacyclin or cytochrome P 450 (CYP) epoxy-genase-derived epoxyeicosatrienoic acids (EETs) contributes to VSM cell hyperpolarization following CH. VSM cell resting membrane potential (Em) was measured in superior mesenteric artery strips isolated from rats with control barometric pressure (PB, ≈630 Torr) and CH (PB, 380

Torr for 48 h). VSM cell Em was normalized between groups following administration of the CYP inhibitors 17-octadecynoic acid and SKF-525A. VSM cell hyperpolarization after CH was not altered by cyclooxygenase inhibition, whereas the selective CYP2C9 inhibitor sulfaphenazole normalized VSM cell Em between groups. Iberiotoxin also normalized VSM cell Em, which suggests that large-conductance, Ca2+-activated K- (BKCa) channel activity is increased after CH. Sulfaphenazole administration restored phenylephrine-induced and myogenic vasoconstriction and Ca2+ responses of mesenteric resistance arteries isolated from CH rats to control levels. Western blot expts. demonstrated that CYP2C9 protein levels were greater in mesenteric arteries from CH rats. In addition, 11,12-EET levels were elevated in endothelial cells from CH rats compared with controls. We conclude that enhanced CYP2C9 expression and 11,12-EET production following CH contributes to BKCa channel-dependent VSM cell hyperpolarization and attenuated vasoreactivity.

=> d iall abeq tech abex 28

L121 ANSWER 28 OF 45 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-698530 [75] WPIX
DOC. NO. CPI: C2002-197743
TITLE: New analogs of 12(R)-hydroxy-5,8,14-**eicosatrienoic** acid are 12(R)-hydroxy-5,8,14-**eicosatrienoic** acid antagonist and agonists used for treating e.g. cancer, inflammatory diseases and cardiovascular disorders.
DERWENT CLASS: B05
INVENTOR(S): FALCK, J R; SCHWARTZMAN, M L; SCHWARTZMAN, M
PATENT ASSIGNEE(S): (FALC-I) FALCK J R; (SCHW-I) SCHWARTZMAN M L; (NYME-N) NEW YORK MEDICAL COLLEGE
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002059072	A2	20020801	(200275)*	EN	68	C07C059-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZW						
US 2002151734	A1	20021017	(200275)			C07C229-24
AU 2002246926	A1	20020806	(200427)			C07C059-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002059072	A2	WO 2002-US46	20020102
US 2002151734	A1 Provisional	US 2001-258806P	20010102
		US 2002-38763	20020102
AU 2002246926	A1	AU 2002-246926	20020102

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002246926	A1 Based on	WO 2002059072

PRIORITY APPLN. INFO: US 2001-258806P 20010102; US 2002-38763 20020102

INT. PATENT CLASSIF.:
MAIN: C07C059-00; C07C229-24

BASIC ABSTRACT:

WO 200259072 A UPAB: 20021120

NOVELTY - 12(R)-hydroxy-5,8,14-**eicosatrienoic** acid (12-HETrE) analogs (I)-(III) are new.

DETAILED DESCRIPTION - 12(R)-hydroxy-5,8,14-**eicosatrienoic** acid (12-HETrE) analogs of formula (I)-(III) are new.

X5, X6, X8, X9, X14-X16 = CH2, CH, C, N, O or S;

R1 = COOH, CH3 or C(O)NHSO2Z;

Z = methyl, paraiodobenzene, COOH, parabenzylamine, propylamine or COOR21;

R21 = 1-6C alkyl;

R11-R13 = H, OH or OCH3;

R20 = CH3 or COOH;

Y = CH2, O, N or S;

X5a, X6a, X8a, X9a, X14a-X16a = CH2, CH, C, N, O or S, and m, n = 0-6.

provided that:

(1) in (I), X5 = X6, X8 = X9 and X14 = X15 or X15 = X16;

(2) in (I), when X5, X8, X14 = CH, Y = CH2, R1 = COOH, R11 and R13 are both H and R20 = CH3, R12 is not OH, and

(3) in (II), when Y = CH2, R1 = COOH and R11 and R13 = H and R12 = OH.

INDEPENDENT CLAIMS are also included for the following:

(A) inhibiting chemotaxis and treating inflammation and ocular conditions which comprises administering a 12-HETrE antagonist and

(B) treating a cardiovascular disorder which comprises administering a 12-HETrE agonist.

ACTIVITY - Antiinflammatory; Dermatological; Antipsoriatic; Virucide; Antibacterial; Antidiabetic; Ophthalmological; Vasotropic; Cerebroprotective; Cardiant; Cytostatic; Antirheumatic; Antiarthritic; Antiallergic; Antigout; Antiulcer; Tranquilizer; Vulnerary; Hypotensive; Antianginal; Antiarrhythmic; Hemostatic.

MECHANISM OF ACTION - 12-HETrE antagonist; 12-HETErE agonist.

In a test, the agonistic activity of 12(R)-hydroxyeicosa-8(Z),14(Z)-dienoic acid was determined by measuring percentage inhibition of (3H)12(R)-HETrE binding at 10 mM to RLME cells. The compound showed 92.4% inhibition.

USE - Used for inhibiting chemotaxis in a cell such as neutrophil, leukocytes or T cells, for treating or preventing inflammation such as skin inflammatory condition, preferably hypersensitization or psoriasis, corneal inflammatory condition, vasodilation, an increase in membrane permeability, early neutrophil chemotaxis and late angiogenesis, ocular conditions preferably corneal angiogenesis, corneal inflammation, corneal transplantation, injury due to prolonged contact lens wear, trachoma, infectious conditions, retinal neovascularization, choroidal neovascularization, retinopathy (e.g. of prematurity or diabetic retinopathy), age-related macular degeneration or caused by viral infection or a bacterial infection, cardiovascular disorders, preferably ischemic conditions, especially stroke, myocardial infarction or coronary artery disease, diabetes or aging and cancer and for inhibiting cell growth in a tumor (all claimed).

The inflammatory diseases also include meningitis, cerebral edema, arthritis, nephritis, adult respiratory distress syndrome, pancreatitis, myositis, neuritis, connective tissue diseases, phlebitis, arteritis, vasculitis, allergy, anaphylaxis, ehrlichiosis, gout, organ transplant

and/or ulcerative colitis. The ocular conditions also include infections, surgical trauma and **hypoxia.** The cardiovascular disorders include hypertension, angina, cardiac arrhythmias, ischemic conditions e.g. chronic exercise or cerebral ischemia or angiogenesis-mediated diseases e.g. solid tumor, blood born tumor (leukemia's tumor metastasis, benign tumors), pre-malignant tumors, rheumatoid arthritis, ocular angiogenic disease, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, Osler-Webber syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma and wound granulation.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-H01; B04-H02J; B04-H04A; B04-H06; B04-H08; B04-N02; B10-A08; B10-B01B; B10-B02B; B10-C02; B10-C03; B10-C04; B10-E04C; B10-E04D; B10-G02; B10-H01; B10-J01; B10-J02; B14-A01; B14-A02; B14-C03; B14-F01; B14-F02; B14-F02C; B14-F02F1; B14-F02F2; B14-G02C; B14-L06; B14-N03; B14-N17; B14-N17B; B14-N17C

TECH UPTX: 20021120

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation is given in the specification.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method (B) also comprises administering an angiogenic factor, preferably angiogenin, angiopoietin-1, Del-1, acidic fibroblast growth factor, basic fibroblast growth factor, follistatin, granulocyte colony-stimulating factor, hepatocyte growth factor, scatter factor, interleukin-8, leptin, midkine, placental growth factor, platelet-derived endothelial cell growth factor, platelet-derived growth factor-BB, pleiotrophin, proliferin, transforming growth factor-alpha, transforming growth factor-beta, tumor necrosis factor-alpha, vascular endothelial growth factor or vascular permeability factor (preferably acidic fibroblast growth factor, basic fibroblast growth factor or vascular endothelial growth factor).

ABEX UPTX: 20021120

SPECIFIC COMPOUNDS - 57 12-HETrE analogs are specifically claimed e.g. 12(R)-hydroxyeicosa-8(Z),14(Z)-dienoic acid (Ia).

ADMINISTRATION - The dosage is 0.1-20 (preferably 1) mg/kg/min intravenously or 0.01-1000 (preferably 50-500) mg/kg/day orally. Administration is also transdermal, intraparenteral, subcutaneous, intramuscular or intracavital.

EXAMPLE - Sodium methoxide (0.59 ml) was added to a solution of benzoic acid 11-methoxycarbonyl-1-oct-2-enyl-undec-4-enyl ester (56.8 mg) in methanol (6.4 ml). After stirring overnight, the mixture was acidified to pH of 5.5 using 1M aqueous oxalic acid (2 ml). All volatiles were removed and residue extracted with AcOEt (30 mlx2). The combined organic extracts were washed and concentrated. The crude residue was dissolved in MeOH (10 ml) and a solution of CH2N2 in diethylether was added at 0degreesC. After stirring for 30 minutes at 0degreesC, the mixture was concentrated and residue purified to give 12(S)-hydroxy-eicosa-8(Z),14(Z)-dienoic acid methyl ester (39 mg).
1M aqueous solution of lithium hydroxide (0.35 ml) was added to this compound (39 mg) in tetrahydrofuran (4.6 ml) and water (0.81 ml). After stirring overnight the reaction mixture was acidified to pH 4.5 with 1M aqueous oxalic acid and worked up to give 12(R)-Hydroxy-eicosa-8(Z),14(Z)-dienoic acid (Ia).

=> d ibib abs 29-
YOU HAVE REQUESTED DATA FROM 17 ANSWERS - CONTINUE? Y/(N):y

L121 ANSWER 29 OF 45 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1996-0234219 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1996 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Inhibition of cytochrome P-450 attenuates **hypoxemia** of acute lung injury in dogs
AUTHOR: STEPHENSON A. H.; SPRAGUE R. S.; WEINTRAUB N. L.; MCMURDO L.; LONIGRO A. J.
CORPORATE SOURCE: Departments of Pharmacological and Physiological Science and Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri 63104, United States
SOURCE: American journal of physiology. Heart and circulatory physiology, **(1996)**, 39(4), H1355-H1362, 32 refs.
ISSN: 0363-6135 CODEN: AJPPDI
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-670D, 354000044343130270
AN 1996-0234219 PASCAL
CP Copyright .COPYRGT. 1996 INIST-CNRS. All rights reserved.
AB The intravenous administration of ethchlorvynol (ECV), in dogs, resulted in an acute lung injury (ALI) characterized by a 200 ± 80% increase in venous admixture and a 142 ± 30% increase in extravascular lung water (EVLW). Pretreatment with the cytochrome P-450 inhibitor 8-methoxypsoralen prevented the ECV-induced increase in venous admixture but not the increased EVLW. These findings parallel those reported for cyclooxygenase inhibition in ECV-induced ALI and suggest that an arachidonic acid (AA) metabolite of pulmonary cytochrome P-450 activity may mediate the increase in venous admixture of ALI. We demonstrate that canine pulmonary microsomes metabolize [1-.sup.1.sup.4C]AA to a variety of products, including the cytochrome P-450 metabolites 5,6-, 8,9-, 11,12-, and 14,15-**epoxyeicosatrienoic** acid (**EET**). In prostaglandin F.sub.2.sub.α-contracted, isolated pulmonary venous rings, 5,6-**EET** induced relaxation in a concentration-dependent manner. This action of 5,6-**EET** was prevented by indomethacin (10.sup.-.sup.5 M). These results suggest that 5,6-**EET** may serve as the cyclooxygenase-dependent endogenous pulmonary vasodilator responsible for the increase in venous admixture of ECV-induced ALI.

L121 ANSWER 30 OF 45 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1980-0227681 PASCAL
TITLE (IN ENGLISH): PGF.sub.2.sub.α, thromboxane B.sub.2 and HETE levels in gerbil brain cortex after ligation of common carotid arteries and decapitation
AUTHOR: SPAGNUOLO C.; SAUTEBIN L.; GALLI G.; RACAGNI G.; GALLI C.; MAZZARI S.; FINESSO M.
CORPORATE SOURCE: Univ. Milan, inst. pharmacol. pharmacognosy, Milan 20129, Italy
SOURCE: Prostaglandins, **(1979)**, 18(1), 53-61, 22 refs.
DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: CNRS-16107
AN 1980-0227681 PASCAL

L121 ANSWER 31 OF 45 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1978-0436175 PASCAL
TITLE: Comparative effects of dihydroergotoxine (**DHET**) on CBF and metabolism changes produced by experimental cerebral edema, **hypoxia** and hypertension.
AUTHOR: CAHN J.; BORZEIX M. G.
CORPORATE SOURCE: Inst. exp. ther. clin. res., F-92120 Montrouge, Fr.
SOURCE: Gerontology, **(1978)**, 24(suppl. 1), 34-42, 10 refs.
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Switzerland
LANGUAGE: English
AVAILABILITY: CNRS-8223
AN 1978-0436175 PASCAL
ABFR La **DHET** perfusee chez le chien presentant un syndrome cerebral per-hypocapnoanemique reduit l'hyperemie cerebrale, augmente la pO.sub.2 veineuse cerebrale et favorise l'oxydation du glucose par le cerveau. La **DHET** peut aussi abaisser les p arterielles moyennes, diastolique et systolique chez les rats avec une hypertension renale presentant un oedeme cerebral induit par intoxication par la triethylation. La **DHET** peut aussi ameliorer les modifications de l'EEG produites par un oedeme traumatique.

L121 ANSWER 32 OF 45 CABA COPYRIGHT 2004 CABI on STN
ACCESSION NUMBER: 95:35410 CABA
DOCUMENT NUMBER: 19951400237
TITLE: Inhibition of human neutrophil leukotriene B4 synthesis in essential fatty acid deficiency: Role of leukotriene A hydrolase
AUTHOR: Cleland, L. G.; James, M. J.; Proudman, S. M.; Neumann, M. A.; Gibson, R. A.
CORPORATE SOURCE: Rheumatology Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia.
SOURCE: Lipids, (**1994**) Vol. 29, No. 3, pp. 151-155. 47 ref.
ISSN: 0024-4201
DOCUMENT TYPE: Journal
LANGUAGE: English
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19950223
AB A woman dependent on long-term total parenteral nutrition developed an aversion and noncompliance to a prescribed weekly lipid infusion designed to meet essential fatty acid (EFA) requirements. Fatty acids (FA) in plasma and isolated peripheral blood neutrophils were analysed in search of biochemical evidence of EFA **deficiency**. Neutrophil 5-**lipoxygenase** metabolism was examined to assess the possible effects of EFA deficiency on neutrophil eicosanoid metabolism. EFA deficiency was confirmed by depletion of linoleic acid and accumulation of **eicosatrienoic** acid (ETrA) in plasma and neutrophil phospholipids. In the neutrophils, ETrA comprised 5.2% of phospholipid FA (normal reference values <0.1%), and arachidonic acid (AA) comprised 8.6% of

phospholipid FA (normal reference range 10-16%). When stimulated by A23187 in vitro on 3 occasions, the woman's neutrophils displayed impaired synthesis of leukotriene B4 (LTB4), but produced normal amounts of 5-hydroxyeicosatetraenoic acid and all-trans isomers of LTB4 formed nonenzymatically from leukotriene A4 (LTA4). This pattern of synthesis suggested inhibition of LTA hydrolase and was also seen in neutrophils from healthy subjects by addition of exogenous ETrA in vitro. Comparative studies of the effects of ETrA and eicosapentaenoic acid on neutrophils in vitro suggested that ETrA is the more potent inhibitor. Accumulation of ETrA, rather than depletion of AA, appears principally responsible for the observed impairment of neutrophil LTB4 synthesis seen in this EFA-deficient subject.

L121 ANSWER 33 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:423379 SCISEARCH
THE GENUINE ARTICLE: 677LW
TITLE: Differential effects of 5,6-**EET** on segmental pulmonary vasoactivity in the rabbit
AUTHOR: Stephenson A H (Reprint); Sprague R S; Losapio J L; Lonigro A J
CORPORATE SOURCE: St Louis Univ, Sch Med, Dept Pharmacol & Physiol Sci, St Louis, MO 63104 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (**JUN 2003**) Vol. 284, No. 6, pp. H2153-H2161.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0363-6135.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the rabbit, 5,6-**epoxyeicosatrienoic** acid (**EET**) was reported both to dilate and to constrict pulmonary blood vessels. We propose that these seemingly contradictory results could be explained by differences in responses to 5,6-**EET** in large-conductance pulmonary arteries (PA) compared with smaller PA and resistance vessels. Thus we found that in rings of extralobar PA [>2-mm outside diameter (OD)], in which active tension had been increased with PGF(2alpha), 5,6-**EET** produced relaxation in a concentration- and cyclooxygenase (COX)-dependent manner. In contrast, 5,6-**EET** increased tension in intralobar (1- to 2-mm OD) PA. Small extralobar PA (2- to 2.5-mm OD) exhibited intermediate responses. In the intact lung, the net effect of 5,6-**EET** (1 x 10(-8)-1 x 10(-5) M) was an increase in pulmonary vascular resistance (PVR) from 13.0 +/- 0.5 to 47.8 +/- 4.6 mmHg.100 ml(-1).min(-1) (EC50 5.9 +/- 1.7 x 10(-7) M). The increase in PVR was accompanied by a 10-fold increase in perfusate thromboxane (TX) B-2 concentration. The 5,6-**EET**-induced increase in PVR was prevented with indomethacin (100 muM), a cyclooxygenase inhibitor, or ONO-3708 (20 muM), a TX/PGH(2) (TP) receptor antagonist, but not with OKY-046 (700 muM), a TX synthase inhibitor. These results demonstrate that although 5,6-**EET** dilates large extralobar PA segments in a COX-dependent manner, in the intact rabbit lung 5,6-**EET** produces constriction that requires synthesis of a COX-dependent agonist of the TP receptor other than TX.

L121 ANSWER 34 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:426317 SCISEARCH
THE GENUINE ARTICLE: 678UZ
TITLE: Chronic **hypoxia** activates lung 15-lipoxygenase, which catalyzes production of 15-HETE and enhances constriction in neonatal rabbit pulmonary arteries
AUTHOR: Zhu D L; Medhora M; Campbell W B; Spitzbarth N; Baker J E; Jacobs E R (Reprint)
CORPORATE SOURCE: Med Coll Wisconsin, Ctr Cardiovasc, Dept Med, 8701 Watertown Plank Rd, Milwaukee, WI 53226 USA (Reprint); Med Coll Wisconsin, Ctr Cardiovasc, Dept Med, Milwaukee, WI 53226 USA; Med Coll Wisconsin, Dept Pharmacol & Toxicol, Milwaukee, WI 53226 USA; Med Coll Wisconsin, Dept Surg, Milwaukee, WI 53226 USA; Med Coll Wisconsin, Dept Pediat Surg, Milwaukee, WI 53226 USA; Med Coll Wisconsin, Cardiovasc Res Ctr, Milwaukee, WI 53226 USA; Harbin Med Coll, Harbin, Peoples R China
COUNTRY OF AUTHOR: USA; Peoples R China
SOURCE: CIRCULATION RESEARCH, (**16 MAY 2003**) Vol. 92, No. 9, pp. 992-1000.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0009-7330.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Hypoxia** causes localized pulmonary arterial (PA) constriction to divert blood flow to optimally ventilated regions of the lung. The biochemical mechanisms for this have remained elusive, especially during prolonged exposures to reduced PO2. We have evidence that subacute **hypoxia** activates 15-lipoxygenase (15-LO) in small PAs of neonatal rabbits maintained for 9 days in **hypoxic** environments (FIO2=0.12) compared with siblings raised under normoxia. PA microsomal products of 15-LO, 15-hydroxyeicosatetraenoic acid (HETE), 11,14,15-**trihydroxyeicosatrienoic** acid (THETA), and 11,12,15-THETA were identified by gas chromatography/mass spectrometry. Increased amounts of these products are synthesized in vivo and in vitro by the lungs of animal raised in **hypoxic** versus normoxic environments. 15-HETE formation is attenuated by lipoxygenase, but not cytochrome P450 or cyclooxygenase inhibitors. Activation of 15-LO is associated with translocation of the enzyme from the cytosol to membrane as seen by Western immunoblotting. Immunohistochemical analysis demonstrates that 15-LO expression is clearly localized in vascular cells in lungs from normoxic and **hypoxic** kits. 15-HETE causes concentration-dependent constriction of PA rings from animals exposed to **hypoxic** but not normoxic environments. In addition, lipoxygenase inhibitors reduce phenylephrine-induced constriction of PA rings. Therefore, subacute **hypoxia** increases expression of and activates 15-LO, and enhances sensitivity of pulmonary arteries to its product, 15-HETE. Because 15-HETE is a constrictor in this vascular bed, it may play an important role in **hypoxia**-induced pulmonary vasoconstriction in rabbit kits. Although a clear causal relationship remains to be demonstrated, these data suggest a previously unrecognized role for 15-LO in **hypoxic** vasoconstriction in neonatal mammals.

L121 ANSWER 35 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:498530 SCISEARCH
THE GENUINE ARTICLE: 687AX
TITLE: Cytochrome P-450 epoxygenase products contribute to

attenuated vasoconstriction after chronic **hypoxia**

AUTHOR: Earley S (Reprint); Pastuszyn A; Walker B R

CORPORATE SOURCE: Univ New Mexico, Hlth Sci Ctr, Dept Cell Biol & Physiol, Vasc Physiol Grp, MSC08 4750, Albuquerque, NM 87131 USA (Reprint); Univ New Mexico, Hlth Sci Ctr, Dept Cell Biol & Physiol, Vasc Physiol Grp, Albuquerque, NM 87131 USA; Univ New Mexico, Hlth Sci Ctr, Dept Biochem & Mol Biol, Albuquerque, NM 87131 USA

COUNTRY OF AUTHOR: USA

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (**JUL 2003**) Vol. 285, No. 1, pp. H127-H136.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0363-6135.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The systemic vasculature exhibits attenuated vasoconstriction following chronic **hypoxia** (CH) that is associated with endothelium-dependent vascular smooth muscle (VSM) cell hyperpolarization. We hypothesized that increased production of arachidonic acid metabolites such as the cyclooxygenase product prostacyclin or cytochrome P-450 (CYP) epoxy-genase-derived **epoxyeicosatrienoic** acids (**EETs**) contributes to VSM cell hyperpolarization following CH. VSM cell resting membrane potential (E-m) was measured in superior mesenteric artery strips isolated from rats with control barometric pressure (PB, congruent to630 Torr) and CH (PB, 380 Torr for 48 h). VSM cell E-m was normalized between groups following administration of the CYP inhibitors 17-octadecynoic acid and SKF-525A. VSM cell hyperpolarization after CH was not altered by cyclooxygenase inhibition, whereas the selective CYP2C9 inhibitor sulfaphenazole normalized VSM cell E-m between groups. Iberiotoxin also normalized VSM cell E-m, which suggests that large-conductance, Ca2+-activated K+ (BKCa) channel activity is increased after CH. Sulfaphenazole administration restored phenylephrine-induced and myogenic vasoconstriction and Ca2+ responses of mesenteric resistance arteries isolated from CH rats to control levels. Western blot experiments demonstrated that CYP2C9 protein levels were greater in mesenteric arteries from CH rats. In addition, 11,12-**EET** levels were elevated in endothelial cells from CH rats compared with controls. We conclude that enhanced CYP2C9 expression and 11,12-**EET** production following CH contributes to BKCa channel-dependent VSM cell hyperpolarization and attenuated vasoreactivity.

L121 ANSWER 36 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:468861 SCISEARCH

THE GENUINE ARTICLE: BW75T

TITLE: Cytochrome P450-derived eicosanoids are mediators of ocular surface inflammation

AUTHOR: Laniado-Schwartzman M (Reprint); Dunn M W

CORPORATE SOURCE: New York Med Coll, Dept Pharmacol, Valhalla, NY 10595 USA (Reprint)

COUNTRY OF AUTHOR: USA

SOURCE: ADVANCES IN PROSTAGLANDIN, LEUKOTRIENE, AND OTHER BIOACTIVE LIPID RESEARCH: BASIC SCIENCE AND CLINICAL APPLICATIONS, (**MAR 2003**) Vol. 525, pp. 47-54.
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013 USA.

ISSN: 0065-2598.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31

L121 ANSWER 37 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:852213 SCISEARCH
THE GENUINE ARTICLE: 728GK
TITLE: Metabolism of 12-hydroperoxyeicosatetraenoic acid to vasodilatory trioxilin C-3 by rabbit aorta
AUTHOR: Pfister S L; Spitzbarth N; Nithipatikom K; Falck J R; Campbell W B (Reprint)
CORPORATE SOURCE: Med Coll Wisconsin, Dept Pharmacol & Toxicol, 8701 Watertown Plank Rd, Milwaukee, WI 53226 USA (Reprint); Med Coll Wisconsin, Dept Pharmacol & Toxicol, Milwaukee, WI 53226 USA; Univ Texas, SW Med Ctr, Dept Biochem, Dallas, TX 75390 USA
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-GENERAL SUBJECTS, (20 JUN 2003) Vol. 1622, No. 1, pp. 6-13.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0304-4165.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 30

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Arachidonic acid is metabolized by both the cyclooxygenase and lipoxygenase pathways by rabbit aorta. We investigated the metabolism of 12-hydroperoxyeicosatetraenoic acid by aortic homogenates and microsomes. Rabbit aortic homogenates were incubated in the presence of C-14-arachidonic acid plus 12-lipoxygenase and analyzed by reversed-phase high-pressure liquid chromatography (HPLC). Under these experimental conditions, there was a 14 C-metabolite that migrated at 17.6 min. This C-14-metabolite was not observed when aortic homogenates were incubated in the **absence** of 12-**lipoxygenase.** Similar results were obtained with aortic microsomes. Further analysis using a different HPLC solvent system resolved the 14 C-metabolite into a number of products. Gas chromatography/mass spectrometric (GC-MS) analysis of the major product (labeled peak 3) after conversion to the methyl ester-trimethylsilyl derivative showed two major compounds (compounds A and B) eluting at 13.99 and 14.14 min. The two compounds differed in the intensities of the 213 and 243 m/z ions with 243 being greater than 213 in compound A and the opposite in compound B (relative abundance 213 vs. 243; 100% vs. 43% for compound A and 5% vs. 100% for compound B). Based on the mass spectra, peak 3 contained two metabolites identified as the methyl ester-trimethylsilyl ether derivatives of 8,11,12-**trihydroxyeicosatrienoic** acid (trioxilin A(3)) and 8,9,12-**trihydroxyeicosatrienoic** acid (trioxilin CA Biological activity of the mixture of two trioxilins isolated from aortic homogenates was tested in phenylephrine-precontracted aortas and found to produce concentration-dependent relaxations (maximal relaxation: 20.1 +/- 7.6%). Further testing with authentic trioxilin A(3) and C-3 revealed that trioxilin C-3 was the active metabolite (maximal relaxation: 16.6 +/- 1.3%). In conclusion, trioxilin C-3 acid was isolated and identified as a novel biologically active arachidonic acid metabolite formed by rabbit aorta when 12-lipoxygenase is supplied exogenously. (C) 2003 Elsevier Science B.V. All rights reserved.

L121 ANSWER 38 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:493645 SCISEARCH
THE GENUINE ARTICLE: 558PM
TITLE: Eicosanoid regulation of vascular endothelial growth factor expression and angiogenesis in microvessel endothelial cells
AUTHOR: Mezentsev A; Seta F; Dunn M W; Ono N; Falck J R; Laniado-Schwartzman M (Reprint)
CORPORATE SOURCE: New York Med Coll, Dept Pharmacol, Basic Sci Bldg 530, Valhalla, NY 10595 USA (Reprint); New York Med Coll, Dept Pharmacol, Valhalla, NY 10595 USA; Univ Texas, SW Med Ctr, Dept Biochem, Dallas, TX 75235 USA; Univ Texas, SW Med Ctr, Dept Pharmacol, Dallas, TX 75235 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (**24 MAY 2002**) Vol. 277, No. 21, pp. 18670-18676.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 12(R)-Hydroxy-5,8,14-**eicosatrienoic** acid (HETrE) is a potent inflammatory and angiogenic eicosanoid in ocular and dermal tissues. Previous studies suggested that 12(R)-HETrE activates microvessel endothelial cells via a high affinity binding site; however, the cellular mechanisms underlying 12(R)-HETrE angiogenic activity are unexplored. Because the synthesis of 12(R)-HETrE is induced in response to **hypoxic** injury, we examined its interactions with vascular endothelial growth factor (VEGF) in rabbit limbal microvessel endothelial cells. Addition of 12(R)-HETrE (0.1 mm) to the cells increased VEGF mRNA levels with maximum 5-fold increase at 45 min. The increase in VEGF mRNA was followed by an increase in immunoreactive VEGF protein. 12(R)-HETrE (0.1 mm) rapidly activated the extracellular signal-regulated kinases (ERKs) ERK1 and ERK2. Moreover, preincubation of cells with PD98059, a selective inhibitor of MEK-1, inhibited 12(R)-HETrE-induced VEGF mRNA. Addition of VEGF antibody to cells grown in Matrigel-coated culture plates inhibited 12(R)-HETrE-induced capillary tube-like formation, suggesting that VEGF mediates, at least in part, the angiogenic response to 12(R)HETrE. The results indicate that in microvessel endothelial cells, 12(R)-HETrE induces VEGF expression via activation of ERK1/2 and that VEGF mediates, at least in part, the angiogenic activity of 12(R)-HETrE. Given the fact that both VEGF and 12(R)-HETrE are produced in the cornea after **hypoxic** injury, their interaction may be an important determinant in the development of neovascularized tissues.

L121 ANSWER 39 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:628940 SCISEARCH
THE GENUINE ARTICLE: 458DW
TITLE: Overexpression of cytochrome P450CYP2J2 protects against **hypoxia**-reoxygenation injury in cultured bovine aortic endothelial cells
AUTHOR: Yang B C; Graham L; Dikalov S; Mason R P; Falck J R; Liao J K; Zeldin D C (Reprint)
CORPORATE SOURCE: NIEHS, Div Intramural Res, NIH, 111 TW Alexander Dr, Bldg 101, Room D236, Res Triangle Pk, NC 27709 USA (Reprint); NIEHS, Div Intramural Res, NIH, Res Triangle Pk, NC 27709

USA; Univ Texas, SW Med Ctr, Dept Biochem, Dallas, TX 75235 USA; Brigham & Womens Hosp, Div Cardiovasc, Boston, MA 02115 USA; Harvard Univ, Sch Med, Boston, MA USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR PHARMACOLOGY, (**AUG 2001**) Vol. 60, No. 2, pp. 310-320.
Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
ISSN: 0026-895X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CYP2J2 is abundant in human heart and its arachidonic acid metabolites, the **epoxyeicosatrienoic** acids (**EETs**), have potent vasodilatory, antiinflammatory and cardioprotective properties. This study was designed to examine the role of CYP2J2 in **hypoxia** -reoxygenation-induced injury in cultured bovine aortic endothelial cells (BAECs). Early passage BAECs were exposed to 24-h **hypoxia** followed by 4-h reoxygenation (HR). HR resulted in cell injury, as indicated by significant increases in lactate dehydrogenase (LDH) release and trypan blue stained cells ($p < 0.01$) and was associated with a decrease in CYP2J2 protein expression. Transfection of BAECs with the CYP2J2 cDNA resulted in increased CYP2J2 expression and arachidonic acid epoxygenase activity, compared with cells transfected with an irrelevant green fluorescent protein (GFP) cDNA. HR induced significant injury in GFP-transfected BAECs, as indicated by increases in LDH release and trypan blue-stained cells ($p < 0.01$); however, the HR-induced injury was markedly attenuated in CYP2J2-transfected cells ($p < 0.01$). HR increased cellular 8-iso-prostaglandin F-2<alpha> ($P < 0.05$), and decreased eNOS expression, L-arginine uptake and conversion, and nitrite production ($p < 0.01$) in GFP-transfected BAECs. CYP2J2 transfection attenuated the HR-induced increase in 8-iso-prostaglandin F-2 alpha ($P < 0.05$) and decreased the amount of extracellular superoxide detected by cytochrome c reduction under normoxic conditions ($p < 0.05$) but did not significantly affect HR-induced decreases in eNOS expression, L-arginine uptake and conversion, and nitrite production. Treatment of BAECs with synthetic **EETs** and/or epoxide hydrolase inhibitors also showed protective effects against FIR injury ($p < 0.05$). These observations suggest: (1) HR results in endothelial injury and decreased CYP2J2 expression; (2) transfection with the CYP2J2 cDNA protects against HR injury; and (3) the cytoprotective effects of CYP2J2 may be mediated, at least in part, by antioxidant effects.

L121 ANSWER 40 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:413832 SCISEARCH
THE GENUINE ARTICLE: 431AW
TITLE: Altered mechanisms underlying **hypoxic** dilation of skeletal muscle resistance arteries of hypertensive versus normotensive Dahl rats
AUTHOR: Frisbee J C (Reprint); Roman R J; Krishna U M; Falck J R; Lombard J H
CORPORATE SOURCE: Med Coll Wisconsin, Dept Physiol, 8701 Watertown Plank Rd, Milwaukee, WI 53226 USA (Reprint); Med Coll Wisconsin, Dept Physiol, Milwaukee, WI 53226 USA; Univ Texas, SW Med Ctr, Dept Biochem, Dallas, TX 75235 USA
COUNTRY OF AUTHOR: USA
SOURCE: MICROCIRCULATION, (**APR 2001**) Vol. 8, No. 2, pp. 115-127.

Publisher: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA.
ISSN: 1073-9688.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: To determine mechanisms underlying **hypoxic** dilation of skeletal muscle resistance arteries from normotensive (NT) and hypertensive (HT) Dahl salt-sensitive (SS) rats.

Methods: Isolateral graeilis arteries (GA) from both rat groups were viewed via television microscopy and vascular responses to a reduction in PO2 from 145 mm Hg to 40 mm Hg were measured with a video micrometer. Responses were determined following endothelium removal and following inhibition of specific biochemical pathways regulating vascular tone.

Results: **Hypoxic** dilation was impaired in HT rats versus NT controls. Endothelium removal abolished **hypoxic** dilation in NT rats, although a significant dilation to **hypoxia** remained in vessels from HT animals. Inhibition of cytochrome P450 (CP450) 4A enzymes blunted **hypoxic** dilation in both groups, while inhibition of **epoxyeicosatrienoic** acid (**EET**) production impaired responses in NT rats only. Inhibition of 20-hydroxyeicosatetraenoic acid (20-HETE) production or blockade of membrane receptors for 20-HETE reduced **hypoxic** dilation in HT rats, with minimal effects in NT animals. Nitric oxide synthase inhibition had no effect on **hypoxic** dilation in either group, while cycloxygenase inhibition significantly reduced this response in both groups.

Conclusions: These results suggest that the mechanisms of **hypoxic** dilation in GA from NT Dahl-SS rats are altered with HT, impairing the response to reduced PO2. While **hypoxia** induced substantial prostanoid release in both groups, the role of CP450 4A enzymes is shifted from **EET** production in NT rats toward inhibition of 20-HETE, production in HT rats.

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ACCESSION NUMBER: 2001:439 SCISEARCH
THE GENUINE ARTICLE: 384MW
TITLE: The lung HETEs (and **EETs**) up
AUTHOR: Jacobs E R (Reprint); Zeldin D C
CORPORATE SOURCE: Med Coll Wisconsin, Dept Physiol & Med, Cardiovasc Res Ctr, 8701 Watertown Plank Rd, Milwaukee, WI 53226 USA (Reprint); Med Coll Wisconsin, Dept Physiol & Med, Cardiovasc Res Ctr, Milwaukee, WI 53226 USA; NIEHS, Pulm Pathobiol Lab, NIH, Res Triangle Pk, NC 27709 USA
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, (**JAN 2001**) Vol. 280, No. 1, pp. H1-H10.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0363-6135.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 115

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Arachidonic acid metabolites of the cyclooxygenase and lipoxygenase pathways have a variety of important lung functions. Recent observations indicate that cytochrome P-450 (P-450) monooxygenases are also expressed in the lung, localized to specific pulmonary cell types (e.g., epithelium,

endothelium, and smooth muscle), and may modulate critical lung functions. This review summarizes recent data on the presence and biological activity of P-450-derived eicosanoids in the pulmonary vasculature and airways, including effects on pulmonary vascular and bronchial smooth muscle tone and airway epithelial ion transport. We hypothesize a number of potential functions of P-450-derived arachidonate metabolites in the lungs such as contribution to **hypoxic** pulmonary vasoconstriction, regulation of bronchomotor tone, control of the composition of airway lining fluid, and limitation of pulmonary inflammation. Finally, we describe a number of emerging technologies, including congenic and transgenic strains of experimental animals, P-450 isoform-specific inhibitors and inhibitory antibodies, eicosanoid analogs, and vectors for delivery of P-450 cDNAs and antisense oligonucleotides. These tools will facilitate further studies on the contribution of endogenously formed P-450 eicosanoid metabolites to lung function, under both normal and pathological conditions.

L121 ANSWER 42 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1999:859268 SCISEARCH
THE GENUINE ARTICLE: 230DT
TITLE: Chronic **hypoxia** induces **epoxyeicosatrienoic** acids (**EETs**) in neonatal rabbit lungs.
AUTHOR: Zhu D (Reprint); Khayat R; Raza T; Tomas L S; Presberg K; Roman R J; Harder D R; Baker J; Jacobs E R
CORPORATE SOURCE: MED COLL WISCONSIN, CVRC, MILWAUKEE, WI 53226
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE , (**MAR 1999**) Vol. 159, No. 3, Supp. [S], pp. A181-A181.
Publisher: AMER LUNG ASSOC, 1740 BROADWAY, NEW YORK, NY 10019.
ISSN: 1073-449X.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L121 ANSWER 43 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:808999 SCISEARCH
THE GENUINE ARTICLE: 120RP
TITLE: Organism reserves in residents of arid zone suffering from ischemic heart disease
AUTHOR: Zunnunov Z R (Reprint)
CORPORATE SOURCE: UZBEK MINIST PUBL HLTH, MED REHABIL & PHYS THERAPY BRANCH, TERMEZ, UZBEKISTAN (Reprint)
COUNTRY OF AUTHOR: UZBEKISTAN
SOURCE: TERAPEVTICHESKII ARKHIV, (**SEP 1998**) Vol. 70, No. 8, pp. 14-17.
Publisher: IZD VO MEDITSINA, PETROVERIGSKII PER 6-8, K-142 MOSCOW, RUSSIA.
ISSN: 0040-3660.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: Russian
REFERENCE COUNT: 9
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Aim. The study of physical performance of ischemic heart disease (IND)

patients in comfortable and uncomfortable (summer) weather conditions.
Materials and methods. Systemic reserves wer
performance tests in comfortable weather (equiv
temperature-**EET** 18-24 degrees C) and in heat dy
EET 25-30 degrees C), i.e. in summer when atmos
low (hyperthermic **hypoxia**).
Results. In uncomfortable weather, compared
performance was significantly reduced evidencin
the cardiovascular system. Comparison of the ma
under the same load provides more accurate defi
in dynamics.
Conclusion. General reserve in IHD patients is reduced under conditions of heart dyscomfort.

L121 ANSWER 44 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 96:886035 SCISEARCH
THE GENUINE ARTICLE: VU893
TITLE: CYP2J subfamily P450s in the lung: Expression, localization, and potential functional significance
AUTHOR: Zeldin D C (Reprint); Foley J; Ma J X; Boyle J E; Pascual J M S; Moomaw C R; Tomer K B; Steenbergen C; Wu S
CORPORATE SOURCE: NIEHS, PULM PATHOBIOL LAB, NIH, POB 12233, RES TRIANGLE PK, NC 27709 (Reprint); NIEHS, LAB EXPT PATHOL, NIH, RES TRIANGLE PK, NC 27709; NIEHS, LAB MOL BIOPHYS, NIH, RES TRIANGLE PK, NC 27709; UNIV N CAROLINA, DEPT MED, CHAPEL HILL, NC 27599; DUKE UNIV, MED CTR, DEPT MED, DURHAM, NC 27719; DUKE UNIV, MED CTR, DEPT PATHOL, DURHAM, NC 27719
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR PHARMACOLOGY, (**NOV 1996**) Vol. 50, No. 5, pp. 1111-1117.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0026-895X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 58
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cytochrome P450 (P450) monooxygenases catalyze the epoxidation of arachidonic acid to form **epoxyeicosatrienoic** acids, which modulate bronchial smooth muscle tone and airway transepithelial ion transport. We recently described a new human P450 arachidonic acid epoxygenase (CYP2J2) and the corresponding rat homologue (CYP2J3). Northern analysis of lung RNA using CYP2J cDNA probes demonstrated that CYP2J2 and CYP2J3 mRNAs were expressed in the lung. Immunoblotting of microsomal fractions prepared from human and rat lungs using a polyclonal antibody raised against recombinant human CYP2J2 revealed a single 56-kDa band confirming abundant pulmonary CYP2J2 and CYP2J3 protein expres sion. Immunohistochemical analysis of formalin-fixed paraffin-embedded human and rat lung sections using the anti-human CYP2J2 IgG and avidin/biotin/peroxidase detection showed that CYP2J proteins were primarily expressed in ciliated epithelial cells lining the airway. Prominent staining was also noted in nonciliated airway epithelial cells, bronchial and pulmonary vascular smooth muscle cells, pulmonary vascular endothelium, and alveolar macrophages, whereas less intense staining was noted in alveolar epithelial cells. Endogenous **epoxyeicosatrienoic** acids were detected in both human and rat lung using gas chromatography/mass spectrometry, thus providing direct evidence for the in vivo human and rat pulmonary P450 metabolism of arachidonic acid. Based

on these data, we conclude that CYP2J2 and CYP2J3 are abundant pulmonary arachidonic acid epoxygenases and that CYP2J products, the **epoxyeicosatrienoic** acids, are endogenous constituents of human and rat lung. In addition to known effects on airway smooth muscle tone and transepithelial electrolyte transport, the localization of CYP2J proteins to vascular smooth muscle and endothelium suggests that **epoxyeicosatrienoic** acids may also be involved in the modulation of pulmonary vascular tone.

L121 ANSWER 45 OF 45 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 78:26 SCISEARCH
THE GENUINE ARTICLE: DZ859
TITLE: COMPARATIVE EFFECTS OF DIHYDROERGOTOXINE (**DHET**) ON CBF AND METABOLISM CHANGES PRODUCED BY EXPERIMENTAL CEREBRAL EDEMA, **HYPOXIA** AND HYPERTENSION
AUTHOR: CAHN J (Reprint); BORZEIX M G
CORPORATE SOURCE: INST EXPTL THERAPY & CLIN RES, F-92120 MONTROUGE, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: GERONTOLOGY, (**1978**) Vol. 24, pp. 34-42.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 11

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:35:31 ON 06 OCT 2004
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FILE 'HCAPLUS' ENTERED AT 13:32:46 ON 06 OCT 2004
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FILE COVERS 1907 - 6 Oct 2004 VOL 141 ISS 15
FILE LAST UPDATED: 5 Oct 2004 (20041005/ED)

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substance identification.

=> fil medlin

FILE 'MEDLINE' ENTERED AT 13:32:49 ON 06 OCT 2004

FILE LAST UPDATED: 5 OCT 2004 (20041005/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> fil biosis

FILE 'BIOSIS' ENTERED AT 13:32:53 ON 06 OCT 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 September 2004 (20040929/ED)

FILE RELOADED: 19 October 2003.

=> fil embase

FILE 'EMBASE' ENTERED AT 13:32:55 ON 06 OCT 2004

FILE COVERS 1974 TO 30 Sep 2004 (20040930/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil pascal

FILE 'PASCAL' ENTERED AT 13:33:01 ON 06 OCT 2004

FILE LAST UPDATED: 4 OCT 2004 <20041004/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

=> fil confsci

FILE 'CONFSCI' ENTERED AT 13:33:09 ON 06 OCT 2004

FILE COVERS 1973 TO 23 Sep 2004 (20040923/ED)

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 13:33:12 ON 06 OCT 2004

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 1, 2004 (20041001/UP).

=>

(FILE 'MEDLINE, EMBASE, BIOSIS, PASCAL, CONFSCI, HCAPLUS' ENTERED AT 13:19:51 ON 06 OCT 2004)

```
=> d que l136
L122        1275 SEA LIAO, K?/AU
L123         366 SEA ZELDIN, D?/AU
L124        1641 SEA (L122 OR L123)
L125        8858 SEA (EET? OR DHET? OR ?ICOSATRIEN?)
L126        6533 SEA (EICOSATRIEN? OR EPOXYEICOSATRIEN? OR DIHYDROXYEICOSATRIEN?
                 )
L127        8881 SEA (L125 OR L126)
L128         179 SEA L124 AND L127
L135          61 DUP REM L128 (118 DUPLICATES REMOVED)
L136          25 SEA L135 AND PY<2000
```

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=> d ibib abs l136 1-
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, BIOSIS, HCAPLUS' - CONTINUE?
(Y)/N:y
```

YOU HAVE REQUESTED DATA FROM 25 ANSWERS - CONTINUE? Y/(N):y

L136 ANSWER 1 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1999387069 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10455056
TITLE: Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids.
AUTHOR: Node K; Huo Y; Ruan X; Yang B; Spiecker M; Ley K; **Zeldin D C**; Liao J K
CORPORATE SOURCE: Vascular Medicine and Atherosclerosis Unit, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, LMRC-322, Boston, MA 02115, USA.
CONTRACT NUMBER: HL-52233 (NHLBI)
HL-58108 (NHLBI)
SOURCE: Science, **(1999 Aug 20)** 285 (5431) 1276-9.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 20020919
Entered Medline: 19990908

AB The **epoxyeicosatrienoic** acids (**EETs**) are products of cytochrome P450 epoxygenases that have vasodilatory properties similar to that of endothelium-derived hyperpolarizing factor. The cytochrome P450 isoform CYP2J2 was cloned and identified as a potential source of **EETs** in human endothelial cells. Physiological concentrations of **EETs** or overexpression of CYP2J2 decreased cytokine-induced endothelial cell adhesion molecule expression, and **EETs** prevented leukocyte adhesion to the vascular wall by a mechanism involving inhibition of transcription factor NF-kappaB and IkappaB kinase. The inhibitory effects of **EETs** were independent of their membrane-hyperpolarizing effects, suggesting that these molecules play an important nonvasodilatory role in vascular inflammation.

L136 ANSWER 2 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1999292745 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10364221
TITLE: Molecular cloning, enzymatic characterization, developmental expression, and cellular localization of a mouse cytochrome P450 highly expressed in kidney.
AUTHOR: Ma J; Qu W; Scarborough P E; Tomer K B; Moomaw C R; Maronpot R; Davis L S; Breyer M D; **Zeldin D C**
CORPORATE SOURCE: Laboratories of Pulmonary Pathobiology, NIEHS, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: P01-DK38226 (NIDDK)
SOURCE: Journal of biological chemistry, **(1999 Jun 18)** 274 (25) 17777-88.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U62294

ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 19990727
Entered Medline: 19990715

AB A cDNA encoding a new cytochrome P450 was isolated from a mouse liver library. Sequence analysis reveals that this 1,886-base pair cDNA encodes a 501-amino acid polypeptide that is 69-74% identical to CYP2J subfamily P450s and is designated CYP2J5. Recombinant CYP2J5 was co-expressed with NADPH-cytochrome P450 oxidoreductase in Sf9 cells using a baculovirus system. Microsomal fractions of CYP2J5/NADPH-cytochrome P450 oxidoreductase-transfected cells metabolize arachidonic acid to 14,15-, 11,12-, and 8, 9-**epoxyeicosatrienoic** acids and 11- and 15-hydroxyeicosatetraenoic acids (catalytic turnover, 4.5 nmol of product/nmol of cytochrome P450/min at 37 degrees C); thus CYP2J5 is enzymologically distinct. Northern analysis reveals that CYP2J5 transcripts are most abundant in mouse kidney and present at lower levels in liver. Immunoblotting using a polyclonal antibody against a CYP2J5-specific peptide detects a protein with the same electrophoretic mobility as recombinant CYP2J5 most abundantly in mouse kidney microsomes. CYP2J5 is regulated during development in a tissue-specific fashion. In the kidney, CYP2J5 is present before birth and reaches maximal levels at 2-4 weeks of age. In the liver, CYP2J5 is absent prenatally and during the early postnatal period, first appears at 1 week, and then remains relatively constant. Immunohistochemical staining of kidney sections with anti-human CYP2J2 IgG reveals that CYP2J protein(s) are present primarily in the proximal tubules and collecting ducts, sites where the **epoxyeicosatrienoic** acids are known to modulate fluid/electrolyte transport and mediate hormonal action. In situ hybridization confirms abundant CYP2J5 mRNA within tubules of the renal cortex and outer medulla. **Epoxyeicosatrienoic** acids are endogenous constituents of mouse kidney thus providing direct evidence for the in vivo metabolism of arachidonic acid by the mouse renal epoxygenase(s). Based on these data, we conclude that CYP2J5 is an enzymologically distinct, developmentally regulated, protein that is localized to specific nephron segments and contributes to the oxidation of endogenous renal arachidonic acid pools. In light of the well documented effects of **epoxyeicosatrienoic** acids in modulating renal tubular transport processes, we postulate that CYP2J5 products play important functional roles in the kidney.

L136 ANSWER 3 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1999128263 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9927620
TITLE: Inhibition of cardiac L-type calcium channels by **epoxyeicosatrienoic** acids.
AUTHOR: Chen J; Capdevila J H; **Zeldin D C**; Rosenberg R L
CORPORATE SOURCE: Department of Cell and Molecular Physiology, University of North Carolina, Chapel Hill, North Carolina, USA.
CONTRACT NUMBER: GM37922 (NIGMS)
HL27430 (NHLBI)
HL49449 (NHLBI)
SOURCE: Molecular pharmacology, **(1999 Feb)** 55 (2) 288-95.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990311

AB **Epoxyeicosatrienoic** acids (**EETs**), products of the cytochrome P-450 monooxygenase metabolism of arachidonic acid, can regulate the activity of ion channels. We examined the effects of **EETs** on cardiac L-type Ca2+ channels that play important roles in regulating cardiac contractility, controlling heart rate, and mediating slow conduction in normal nodal cells and ischemic myocardium. Our experimental approach was to reconstitute porcine L-type Ca2+ channels into planar lipid bilayers where we could control the aqueous and lipid environments of the channels and the regulatory pathways that change channel properties. We found that 20 to 125 nM **EETs** inhibited the open probability of reconstituted L-type Ca2+ channels, accelerated the inactivation of the channels, and reduced the unitary current amplitude of open channels. There was no selectivity among different **EET** regioisomers or stereoisomers. When 11,12-**EET** was esterified to the sn-2 position of phosphatidylcholine, restricting it to the hydrophobic phase of the planar lipid bilayer, the reconstituted channels were similarly inhibited, suggesting that the **EET** interacts directly with Ca2+ channels through the lipid phase. The inhibitory effects of **EET** persisted in the presence of microcystin, an inhibitor of protein phosphatases 1 and 2A, suggesting that dephosphorylation was not the mechanism through which these eicosanoids down-regulate channel activity. This inhibition may be an important protective mechanism in the setting of cardiac ischemia where arachidonic acid levels are dramatically increased and **EETs** have been shown to manifest preconditioning-like effects.

L136 ANSWER 4 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1998401042 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9730909
TITLE: Nutritional status modulates rat liver cytochrome P450 arachidonic acid metabolism.
AUTHOR: Qu W; Rippe R A; Ma J; Scarborough P; Biagini C; Fiedorek F T; Travlos G S; Parker C; **Zeldin D C**
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: P30-DK34987 (NIDDK)
R29-AA10459 (NIAAA)
SOURCE: Molecular pharmacology, **(1998 Sep)** 54 (3) 504-13.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981005

AB Alterations in nutritional status affect hepatic cytochrome P450 levels. Since cytochromes P450 participate in the metabolism of arachidonic acid, we hypothesized that changes in liver P450 arachidonic acid metabolism occur during fasting and refeeding. Male Fisher 344 rats were either fed, fasted 48 hr (F48), fasted 48 hr and then refed 6 hr (F48/R6), or fasted 48 hr and then refed 24 hr (F48/R24). F48 rats had reduced body weight, increased plasma beta-hydroxybutyrate, and reduced plasma insulin compared with the other groups. Although there was no significant change in total liver P450 content, there was a significant 20%, 48%, and 24% reduction in total hepatic microsomal arachidonic acid metabolism in F48, F48/R6, and F48/R24 rats, respectively, compared with fed rats. Epoxygenase activity decreased by 28%, 51%, and 26% in F48, F48/R6, and F48/R24 rats,

respectively. In contrast, omega-1 hydroxylase activity increased by 126% in F48 rats compared with fed rats. Immunoblotting revealed that levels of CYP2C11 protein were markedly reduced, whereas levels of CYP2E1 protein were markedly increased in the F48 and F48/R6 groups. In contrast, levels of CYP1A1, CYP1A2, CYP2B1, CYP2J3, CYP4A1, and CYP4A3 were unchanged with fasting/refeeding. Northern blots revealed that levels of CYP2C11 mRNAs were decreased, whereas CYP2E1 mRNAs were increased in F48 and F48/R6 rats. Recombinant CYP2C11 metabolized arachidonic acid primarily to epoxides with preference for the 14(S),15(R)-, 11(R), 12(S)-, and 8(S),9(R)- **epoxyeicosatrienoic** acid enantiomers. We conclude that (1) nutritional status affects hepatic microsomal arachidonic acid metabolism, (2) reduced epoxygenase activity in F48 and F48/R6 rats is accompanied by decreased levels of CYP2C11, (3) increased omega-1 hydroxylase activity is accompanied by augmented levels of CYP2E1, and (4) the effects of fasting on CYP2C11 and CYP2E1 expression occur at the pretranslational level.

L136 ANSWER 5 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1998389577 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9721182
TITLE: Cloning and expression of murine CYP2Cs and their ability to metabolize arachidonic acid.
AUTHOR: Luo G; **Zeldin D C**; Blaisdell J A; Hodgson E; Goldstein J A
CORPORATE SOURCE: Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina 27709, USA.
SOURCE: Archives of biochemistry and biophysics, **(1998 Sep 1)** 357 (1) 45-57.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF047542; GENBANK-AF047725; GENBANK-AF047726; GENBANK-AF047727
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 19981006
Entered Medline: 19980921

AB Five murine cytochrome P450 (CYP) 2C cDNAs were cloned and characterized, including four new members of this subfamily: CYP2C37, CYP2C38, CYP2C39, and CYP2C40. The cDNAs ranged from 1716 to 1812 bp in length and encoded polypeptides of 490 amino acid residues except for CYP2C40, which contained an additional glutamic acid residue at the carboxyl terminus. The amino acid identity of the murine CYP2Cs ranged from 69 to 92%, while the overall amino acid identity was 60%; however, within the six putative substrate recognition sites the identity was only 25 to 41%, suggesting possible differences in substrate specificity and product profiles. The CYP2C cDNAs were expressed in Escherichia coli following modification of the N-terminus. All five recombinant CYP2Cs metabolized arachidonic acid, but with different metabolic profiles and catalytic rates. Based on coelution with authentic standards on reverse-phase HPLC, themajor metabolites were tentatively identified asfollows: CYP2C29 and CYP2C39 produced 14, 15-cis-**epoxyeicosatrienoic** acid (**EET**); CYP2C37 produced 12-hydroxyeicosatetraenoic acid (HETE); CYP2C38 produced 11,12-**EET**; and CYP2C40 produced an unidentified metabolite that coeluted with 16-,17-, and 18-HETEs. The turnover numbers for CYP2C29, CYP2C37, CYP2C38, CYP2C39, and CYP2C40 were 0.34, 1.12, 5.15, 0.51, and 0.15 nmol/nmol/min, respectively. Reverse transcriptase-polymerase chain

reaction demonstrated the presence of CYP2C29 mRNA in liver as well as in extrahepatic tissues including brain, kidney, lung, heart, and intestine. CYP2C38 and CYP2C40 were found in liver, brain, kidney, and intestine, with trace amounts in lung and heart, while CYP2C37 and CYP2C39 appeared to be liver specific.

L136 ANSWER 6 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1998362054 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9694933
TITLE: Epoxygenase metabolites of arachidonic acid affect electrophysiologic properties of rat tracheal epithelial cells1.
AUTHOR: Pascual J M; McKenzie A; Yankaskas J R; Falck J R; **Zeldin D C**
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: DK46004 (NIDDK)
GM31278 (NIGMS)
NO1-ES-35357 (NIEHS)
SOURCE: Journal of pharmacology and experimental therapeutics, **(1998 Aug)** 286 (2) 772-9.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980902

AB **Epoxyeicosatrienoic** acids (**EETs**) and **dihydroxyeicosatrienoic** acids, products of the cytochrome P450 arachidonic acid epoxygenase pathway, have been shown to affect electrolyte transport in the kidney; however, the effects of these compounds on airway epithelial ion transport have not been investigated. Intact rat tracheas and primary cultures of rat tracheal epithelial cells were mounted in Ussing chambers to monitor changes in transepithelial voltage (Vt), short circuit current (Isc) and electrical resistance (Rt), with or without the addition of increasing concentrations (10(-9)-10(-6) M) of arachidonic acid, each of the four regioisomeric **EETs** and each of the corresponding **dihydroxyeicosatrienoic** acids. In intact tracheas, 11,12-**EET** caused dose-dependent decreases in Vt and Isc (DeltaVt = 0. 4 +/- 0.1 mV, DeltaIsc = -16.9 +/- 5.4 microA/cm2 at 10(-6) M, P < . 05 vs. vehicle), whereas changes in Rt were not significantly different than vehicle alone. 11,12-**dihydroxyeicosatrienoic** acid caused less impressive decreases in Vt and Isc, although arachidonic acid and the other compounds tested were without significant effects. 11,12-**EET** induced similar changes in cultured tracheal epithelial cell electrical parameters at concentrations as low as 10(-9) M. The effects of 11,12-**EET** were highly stereoselective, with activity limited to 11(R),12(S)-**EET**, the least abundant rat lung enantiomer. Pretreatment with amiloride or mucosal exposure to sodium free media did not significantly alter the 11,12-**EET**-induced changes in Vt. In contrast, pretreatment with bumetanide abolished the 11,12-**EET** electrophysiologic effects, suggesting that these effects may be mediated through inhibition of a chloride conductive pathway. We conclude that arachidonic acid epoxygenase metabolites cause significant changes in rat

airway electrical parameters and may be involved in the control of lung fluid and electrolyte transport.

L136 ANSWER 7 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1998269806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9606961
TITLE: Arachidonic acid metabolism in the marine fish Stenotomus chrysops (Scup) and the effects of cytochrome P450 1A inducers.
AUTHOR: Schlezinger J J; Parker C; **Zeldin D C**; Stegeman J J
CORPORATE SOURCE: Biology Department, Woods Hole Oceanographic Institution, Massachusetts 02543, USA.
CONTRACT NUMBER: P42-ES07381 (NIEHS)
SOURCE: Archives of biochemistry and biophysics, **(1998 May 15)** 353 (2) 265-75.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980618

AB Cytochrome P450-mediated arachidonic acid (AA) metabolism was investigated in the marine fish scup, Stenotomus chrysops. Liver microsomes incubated with AA and NADPH produced **epoxyeicosatrienoic** acids (**EETs**) and their hydration products (**dihydroxyeicosatrienoic** acids, **DHETs**), midchain conjugated dienols (midchain HETEs), and C16-through C20-alcohols of AA (omega-terminal HETEs), all identified by HPLC and GC/MS. Gravid females had 4-fold lower AA metabolism rates than males but identical metabolite profiles. The 5,6-**EET** (inferred from stable metabolites) was most abundant (47% of total **EETs**) followed by 14,15-, 11,12-, and 8,9-**EET** (27, 13, and 13%, respectively). The 12-HETE represented 25% of total HETEs followed in abundance by 16-, 15-, 11-, 19-, 20-, 8-, and 9-HETE. Antibodies against scup CYP1A and a scup CYP2B-like protein inhibited liver microsomal AA metabolism by 30 and 46%, respectively. GC/MS analysis revealed **EETs** and **DHETs** as endogenous constituents in scup liver; the predominant **EETs** were 8,9- and 14,15-**EET**, followed by a lesser amount of 11,12-**EET**. Chiral analysis showed a preference for the S,R-enantiomers of endogenous 8,9-, 11,12-, and 14,15-**EET** (optical purities 80, 64, and 64%, respectively). Treatment of scup with the CYP1A inducer benzo(a)pyrene (BP) increased liver microsomal formation of **EETs** and HETEs by 2.7-fold in spring and 1.7-fold in summer. BP treatment did not affect microsomal **EET** regioselectivity, but shifted hydroxylation in favor of 19-HETE and induced 17-HETE formation. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) treatment in summer did not induce liver microsomal AA metabolism rates, yet BP and TCDD both increased endogenous **EET** content of liver (5- and 3-fold, respectively), with a shift to 14,15-**EET**. BP treatment increased the selectivity for the S,R-enantiomers of endogenous 8,9-, 11,12-, and 14,15-**EET** (optical purities 91, 84, and 83%, respectively). Kidney, gill, and heart microsomes all metabolized AA, at rates 10- to 30-fold less than liver microsomes. Similar amounts of endogenous 8,9- and 14,15-**EET** and less 11,12-**EET** were detected in heart and kidney, and there was a strong enantioselectivity for 8(R),9(S)-**EET** in heart (optical purity 78%) but not in

kidney. BP treatment did not alter the total **EET** content in these organs but did shift the regiochemical profile in heart to favor 14,15-**EET**. Thus, scup liver and extrahepatic organs metabolize AA via multiple cytochrome P450 (CYP) forms to eicosanoids in vitro and in vivo. BP or TCDD induced endogenous AA metabolism in liver, altering **EET** regioselectivity and, with BP, stereoselectivity. While AhR agonists alter metabolism of AA in early diverging vertebrates expressing both CYP1A and AhR, the magnitude of effects may depend upon the type of inducer.

L136 ANSWER 8 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97330824 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9187259
TITLE: CYP2J subfamily cytochrome P450s in the gastrointestinal tract: expression, localization, and potential functional significance.
AUTHOR: **Zeldin D C**; Foley J; Goldsworthy S M; Cook M E; Boyle J E; Ma J; Moomaw C R; Tomer K B; Steenbergen C; Wu S
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.. zeldin@niehs.nih.gov
CONTRACT NUMBER: P50-AG05128 (NIA)
SOURCE: Molecular pharmacology, **(1997 Jun)** 51 (6) 931-43. Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970714

AB Our laboratory recently described a new human cytochrome P450 arachidonic acid epoxygenase (CYP2J2) and the corresponding rat homologue (CYP2J3), both of which were expressed in extrahepatic tissues. Northern analysis of RNA prepared from the human and rat intestine demonstrated that CYP2J2 and CYP2J3 mRNAs were expressed primarily in the small intestine and colon. In contrast, immunoblotting studies using a polyclonal antibody raised against recombinant CYP2J2 showed that CYP2J proteins were expressed throughout the gastrointestinal tract. Immunohistochemical staining of formalin-fixed, paraffin-embedded intestinal sections using anti-CYP2J2 IgG and avidin-biotin-peroxidase detection revealed that CYP2J proteins were present at high levels in nerve cells of autonomic ganglia, epithelial cells, intestinal smooth muscle cells, and vascular endothelium. The distribution of this immunoreactivity was confirmed by in situ hybridization using a CYP2J2-specific antisense RNA probe. Microsomal fractions prepared from human jejunum catalyzed the NADPH-dependent metabolism of arachidonic acid to **epoxyeicosatrienoic** acids as the principal reaction products. Direct evidence for the in vivo epoxidation of arachidonic acid by intestinal cytochrome P450 was provided by documenting, for the first time, the presence of **epoxyeicosatrienoic** acids in human jejunum by gas chromatography/mass spectrometry. We conclude that human and rat intestine contain an arachidonic acid epoxygenase belonging to the CYP2J subfamily that is localized to autonomic ganglion cells, epithelial cells, smooth muscle cells, and vascular endothelium. In addition to the known effects on intestinal vascular tone, we speculate that CYP2J products may be involved in the release of intestinal neuropeptides, control of intestinal motility, and/or modulation of intestinal fluid/electrolyte transport.

L136 ANSWER 9 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97284730 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9139707
TITLE: Molecular cloning, expression, and functional significance of a cytochrome P450 highly expressed in rat heart myocytes.
AUTHOR: Wu S; Chen W; Murphy E; Gabel S; Tomer K B; Foley J; Steenbergen C; Falck J R; Moomaw C R; **Zeldin D C**
CORPORATE SOURCE: From, NIEHS, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: GM31278 (NIGMS)
HL39752 (NHLBI)
SOURCE: Journal of biological chemistry, **(1997 May 9)** 272 (19) 12551-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970616

AB A cDNA encoding a P450 monooxygenase was amplified from reverse transcribed rat heart and liver total RNA by polymerase chain reaction using primers based on the 5'- and 3'-end sequences of two rat pseudogenes, CYP2J3P1 and CYP2J3P2. Sequence analysis revealed that this 1,778-base pair cDNA contained an open reading frame and encoded a new 502 amino acid protein designated CYP2J3. Based on the deduced amino acid sequence, CYP2J3 was approximately 70% homologous to both human CYP2J2 and rabbit CYP2J1. Recombinant CYP2J3 protein was co-expressed with NADPH-cytochrome P450 oxidoreductase in Sf9 insect cells using a baculovirus expression system. Microsomal fractions of CYP2J3/NADPH-cytochrome P450 oxidoreductase-transfected cells metabolized arachidonic acid to 14,15-, 11,12-, and 8, 9-**epoxyeicosatrienoic** acids and 19-hydroxyeicosatetraenoic acid as the principal reaction products (çatalytic turnover, 0.2 nmol of product/nmol of cytochrome P450/min at 37 degrees C). Immunoblotting of microsomal fractions prepared from rat tissues using a polyclonal antibody raised against recombinant CYP2J2 that cross-reacted with CYP2J3 but not with other known rat P450s demonstrated abundant expression of CYP2J3 protein in heart and liver. Immunohistochemical staining of formalin-fixed paraffin-embedded rat heart tissue sections using the anti-CYP2J2 IgG and avidin-biotin-peroxidase detection localized expression of CYP2J3 primarily to atrial and ventricular myocytes. In an isolated-perfused rat heart model, 20 min of global ischemia followed by 40 min of reflow resulted in recovery of only 44 +/- 6% of base-line contractile function. The addition of 5 microM 11, 12-**epoxyeicosatrienoic** acid to the perfusate prior to global ischemia resulted in a significant 1.6-fold improvement in recovery of cardiac contractility (69 +/- 5% of base line, p = 0.01 versus vehicle alone). Importantly, neither 14,15-**epoxyeicosatrienoic** acid nor 19-hydroxyeicosatetraenoic acid significantly improved functional recovery following global ischemia, demonstrating the specificity of the biological effect for the 11, 12-**epoxyeicosatrienoic** acid regioisomer. Based on these data, we conclude that (a) CYP2J3 is one of the predominant enzymes responsible for the oxidation of endogenous arachidonic acid pools in rat heart myocytes and (b) 11,12-**epoxyeicosatrienoic** acid may play an important functional role in the response of the heart to ischemia.

L136 ANSWER 10 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97200815 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9048644
TITLE: Predominant expression of an arachidonate epoxygenase in islets of Langerhans cells in human and rat pancreas.
AUTHOR: **Zeldin D C**; Foley J; Boyle J E; Moomaw C R; Tomer K B; Parker C; Steenbergen C; Wu S
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.. ZELDIN@NIEHS.NIH.GOV
SOURCE: Endocrinology, **(1997 Mar)** 138 (3) 1338-46.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 19970422
Entered Medline: 19970407

AB Our laboratory recently described a new human cytochrome P450 arachidonic acid epoxygenase (CYP2J2) and the corresponding rat homolog (CYP2J3). Immunoblotting studies using a polyclonal antibody raised against recombinant human CYP2J2 confirmed CYP2J protein expression in human and rat pancreatic tissues. Immunohistochemical staining of formalin-fixed paraffin-embedded rat and human pancreas using the anti-CYP2J2 IgG and avidin-biotin-peroxidase detection revealed that CYP2J2 protein expression was highly localized to cells in the islets of Langerhans, with minimal staining in pancreatic exocrine cells. Colocalization studies using antibodies to the glucagon, insulin, somatostatin, and pancreatic polypeptide as markers for alpha-, beta-, delta-, and PP cells, respectively, showed that CYP2J protein expression was abundantly present in all four cell types, but was highest in the glucagon-producing alpha-cells. Direct evidence for the epoxidation of arachidonic acid by pancreatic cytochrome P450 was provided by documenting, for the first time, the presence of **epoxyeicosatrienoic** acids in vivo in human and rat pancreas by gas chromatography/mass spectrometry. Importantly, the levels of immunoreactive CYP2J2 in different human pancreatic tissues were highly correlated with endogenous **epoxyeicosatrienoic** acid concentrations. We conclude that human and rat pancreas contain an arachidonic acid epoxygenase belonging to the CYP2J subfamily that is highly localized to islet cells. These data together with previous work showing effects of **epoxyeicosatrienoic** acids in stimulating insulin and glucagon secretion from isolated rat pancreatic islets support the hypothesis that epoxygenase products may be involved in stimulus-secretion coupling in the pancreas.

L136 ANSWER 11 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97070416 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8913342
TITLE: CYP2J subfamily P450s in the lung: expression, localization, and potential functional significance.
AUTHOR: **Zeldin D C**; Foley J; Ma J; Boyle J E; Pascual J M; Moomaw C R; Tomer K B; Steenbergen C; Wu S
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.. zeldin@niehs.nih.gov
CONTRACT NUMBER: N01-ES35356 (NIEHS)

P50-AG05128 (NIA)
SOURCE: Molecular pharmacology, **(1996 Nov)** 50 (5) 1111-7.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961226

AB Cytochrome P450 (P450) monooxygenases catalyze the epoxidation of arachidonic acid to form **epoxyeicosatrienoic** acids, which modulate bronchial smooth muscle tone and airway transepithelial ion transport. We recently described a new human P450 arachidonic acid epoxygenase (CYP2J2) and the corresponding rat homologue (CYP2J3). Northern analysis of lung RNA using CYP2J cDNA probes demonstrated that CYP2J2 and CYP2J3 mRNAs were expressed in the lung. Immunoblotting of microsomal fractions prepared from human and rat lungs using a polyclonal antibody raised against recombinant human CYP2J2 revealed a single 56-kDa band confirming abundant pulmonary CYP2J2 and CYP2J3 protein expression. Immunohistochemical analysis of formalin-fixed paraffin-embedded human and rat lung sections using the anti-human CYP2J2 IgG and avidin/biotin/peroxidase detection showed that CYP2J proteins were primarily expressed in ciliated epithelial cells lining the airway. Prominent staining was also noted in nonciliated airway epithelial cells, bronchial and pulmonary vascular smooth muscle cells, pulmonary vascular endothelium, and alveolar macrophages, whereas less intense staining was noted in alveolar epithelial cells. Endogenous **epoxyeicosatrienoic** acids were detected in both human and rat lung using gas chromatography/mass spectrometry, thus providing direct evidence for the in vivo human and rat pulmonary P450 metabolism of arachidonic acid. Based on these data, we conclude that CYP2J2 and CYP2J3 are abundant pulmonary arachidonic acid epoxygenases and that CYP2J products, the **epoxyeicosatrienoic** acids, are endogenous constituents of human and rat lung. In addition to known effects on airway smooth muscle tone and transepithelial electrolyte transport, the localization of CYP2J proteins to vascular smooth muscle and endothelium suggests that **epoxyeicosatrienoic** acids may also be involved in the modulation of pulmonary vascular tone.

L136 ANSWER 12 OF 25 MEDLINE on STN
ACCESSION NUMBER: 96230244 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8651708
TITLE: Biochemical characterization of the human liver cytochrome P450 arachidonic acid epoxygenase pathway.
AUTHOR: **Zeldin D C**; Moomaw C R; Jesse N; Tomer K B; Beetham J; Hammock B D; Wu S
CORPORATE SOURCE: Laboratories of Pulmonary Pathology and Molecular Biophysics, National Institute of Environmental Sciences, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: ES 02710 (NIEHS)
NOK 38226
SOURCE: Archives of biochemistry and biophysics, **(1996 Jun 1)** 330 (1) 87-96.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960805
Last Updated on STN: 19970203
Entered Medline: 19960722

AB Human liver microsomal fractions metabolized arachidonic acid in the presence of NADPH yielding **epoxyeicosatrienoic** acids and their hydration products, **dihydroxyeicosatrienoic** acids, as the principal reaction products. Inhibition studies using polyclonal antibodies prepared against recombinant CYP2C8, an abundant human liver cytochrome P450 epoxygenase, demonstrated 85-90% inhibition of arachidonic acid epoxide formation. Both **epoxyeicosatrienoic** acids and **dihydroxyeicosatrienoic** acids were detected in large amounts in human liver using gas chromatography/mass spectrometry. Chiral analysis of the endogenous liver epoxides demonstrated a preference for the 14(R),15(S)-, 11(R),12(S)-, and 8(S),9(R)-**epoxyeicosatrienoic** acid enantiomers. Importantly, the chirality of liver **epoxyeicosatrienoic** acids matched that previously reported for recombinant CYP2C8 (Zeldin et al. (1995) Arch. Biochem. Biophys. 322, 76-86). Incubations of both human liver cytosolic and microsomal fractions with synthetic **epoxyeicosatrienoic** acids revealed a 10-fold higher rate of **dihydroxyeicosatrienoic** acid formation with cytosolic relative to microsomal fractions. Recombinant human liver cytosolic epoxide hydrolase rapidly and regioselectively hydrated **epoxyeicosatrienoic** acids. We conclude, based on these data, that CYP2C8 is one of the primary, constitutive hepatic arachidonic acid epoxygenases responsible for formation of **epoxyeicosatrienoic** acids and that cytosolic epoxide hydrolase is the principal liver enzyme which forms the **dihydroxyeicosatrienoic** acids. We speculate that these biologically active eicosanoids may be important in maintaining homeostasis in the liver.

L136 ANSWER 13 OF 25 MEDLINE on STN
ACCESSION NUMBER: 96216439 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8631948
TITLE: Molecular cloning and expression of CYP2J2, a human cytochrome P450 arachidonic acid epoxygenase highly expressed in heart.
AUTHOR: Wu S; Moomaw C R; Tomer K B; Falck J R; **Zeldin D C**
CORPORATE SOURCE: Laboratory of Pulmonary Pathobiology, NIEHS, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.
CONTRACT NUMBER: GM31278 (NIGMS)
GM37922 (NIGMS)
SOURCE: Journal of biological chemistry, **(1996 Feb 16)** 271 (7) 3460-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U37143
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19980206
Entered Medline: 19960702

AB A cDNA encoding a human cytochrome P450 arachidonic acid epoxygenase was isolated from a human liver cDNA library. Sequence analysis revealed that this 1,876-base pair cDNA contained an open reading frame and encoded a new 502-amino acid protein designated CYP2J2. Blot hybridization analysis of RNA prepared from human tissues revealed that CYP2J2 was highly

expressed in the heart. Recombinant CYP2J2 protein was prepared using the baculovirus expression system and purified to near electrophoretic homogeneity. The enzyme metabolized arachidonic acid predominantly via olefin epoxidation to all four regioisomeric cis-**epoxyeicosatrienoic** acids (catalytic turnover 65 pmol of product formed/nmol of cytochrome P450/min at 30 degrees C). Epoxidation of arachidonic acid by CYP2J2 at the 14,15-olefin was highly enantioselective for (14R, 15S)-**epoxyeicosatrienoic** acid (76% optical purity). Immunoblotting of microsomal fractions prepared from human tissues using a polyclonal antibody raised against the recombinant hemoprotein confirmed primary expression of CYP2J2 protein in human heart. The in vivo significance of CYP2J2 was suggested by documenting the presence of **epoxyeicosatrienoic** acids in the human heart using gas chromatography/mass spectroscopy. Importantly, the chirality of CYP2J2 products matched that of the **epoxyeicosatrienoic** acid enantiomers present, in vivo, in human heart. We propose that CYP2J2 is one of the enzymes responsible for epoxidation of endogenous arachidonic acid pools in human heart and that **epoxyeicosatrienoic** acids may, therefore, play important functional roles in cardiac physiology.

L136 ANSWER 14 OF 25 MEDLINE on STN
ACCESSION NUMBER: 96004782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7574697
TITLE: Molecular cloning, expression and characterization of an endogenous human cytochrome P450 arachidonic acid epoxygenase isoform.
AUTHOR: **Zeldin D C**; DuBois R N; Falck J R; Capdevila J H
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee 37232, USA.
CONTRACT NUMBER: HL07123 (NHLBI)
NIHDK 38226 (NICHD)
SOURCE: Archives of biochemistry and biophysics, **(1995 Sep 10)** 322 (1) 76-86.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951023

AB A cDNA containing an open reading frame coding for a human cytochrome P450 arachidonic acid epoxygenase was isolated from a male human kidney cDNA library. Sequence analysis showed that, with few exceptions, this cDNA was nearly identical to the published sequence for human liver Cyp 2C8 (S. T. Okino et al., 1987, J. Biol. Chemical 262, 16072-16079) and encoded a polypeptide of 490 amino acids. Nucleic acid hybridization indicated that: (a) Cyp 2C8 and 2C10 were expressed at comparable levels in the human liver and (b) compared to Cyp 2C10, the steady state concentrations of Cyp 2C8 transcripts in the human kidney were substantially lower. The kidney 2C8 cDNA was cloned into a pBlue BacIII vector, expressed using a baculovirus/Sf9 insect cell system, and the recombinant Cyp 2C8 protein was purified by a combination of hydrophobic and hydroxylapatite chromatography. Purified recombinant Cyp 2C8 and 2C10 were reconstituted in the presence of NADPH and NADPH-cytochrome P450 reductase and shown to metabolize arachidonic via olefin epoxidation with both proteins generating, almost exclusively, epoxygenase-derived products (94 and 90% of total products, respectively). Catalytic turnover (1.05 and 0.75 nmol of product/nmol of hemoprotein/min at 30 degrees C for Cyp 2C8 and 2C10,

respectively) was inhibited by the addition of purified cytochrome b5. Metabolism by recombinant 2C8 was both regio- and enantioselective for 11(R), 12(S)- and 14(R), 15(S)-**epoxyeicosatrienoic** acids (82% optical purity, each). Compared to Cyp 2C8, arachidonic acid epoxidation by Cyp 2C10 was less regio- and stereo-selective and generated mixtures of 8(S), 9(R)-, 11(S), 12(R)-, and 14(R), 15(S)-**epoxyeicosatrienoic** acids (with optical purities of 66, 69, 63%, respectively). Importantly, recombinant Cyp 2C8 and 2C10 epoxidized the arachidonic acid 11, 12-olefin with opposite enantiofacial selectivities. Only for Cyp 2C8 did the chirality of the products match that of the enantiomers present, in vivo, in human kidney cortex (A. Karara et al., 1990, FEBS Lett. 268, 227-230). Hence, we propose that Cyp 2C8 is one of the human cytochrome P450 isoforms responsible for the metabolism of endogenous arachidonic acid pools.

L136 ANSWER 15 OF 25 MEDLINE on STN
ACCESSION NUMBER: 95256438 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7738183
TITLE: The rabbit pulmonary cytochrome P450 arachidonic acid metabolic pathway: characterization and significance.
AUTHOR: **Zeldin D C**; Plitman J D; Kobayashi J; Miller R F; Snapper J R; Falck J R; Szarek J L; Philpot R M; Capdevila J H
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee 37232, USA.
CONTRACT NUMBER: GM37922 (NIGMS)
HL07123 (NHLBI)
HL27274 (NHLBI)
+
SOURCE: Journal of clinical investigation, **(1995 May)** 95 (5) 2150-60.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19970203
Entered Medline: 19950605

AB Cytochrome P450 metabolizes arachidonic acid to several unique and biologically active compounds in rabbit liver and kidney. Microsomal fractions prepared from rabbit lung homogenates metabolized arachidonic acid through cytochrome P450 pathways, yielding cis-**epoxyeicosatrienoic** acids (**EETs**) and their hydration products, vic-**dihydroxyeicosatrienoic** acids, mid-chain cis-trans conjugated dienols, and 19- and 20-hydroxyeicosatetraenoic acids. Inhibition studies using polyclonal antibodies prepared against purified CYP2B4 demonstrated 100% inhibition of arachidonic acid epoxide formation. Purified CYP2B4, reconstituted in the presence of NADPH-cytochrome P450 reductase and cytochrome b5, metabolized arachidonic acid, producing primarily **EETs**. **EETs** were detected in lung homogenate using gas chromatography/mass spectroscopy, providing evidence for the in vivo pulmonary cytochrome P450 epoxidation of arachidonic acid. Chiral analysis of these lung **EETs** demonstrated a preference for the 14(R),15(S)-, 11(S),12(R)-, and 8(S),9(R)-**EET** enantiomers. Both **EETs** and vic-**dihydroxyeicosatrienoic** acids were detected in bronchoalveolar lavage fluid. At micromolar concentrations, methylated 5,6-**EET** and 8,9-**EET** significantly relaxed histamine-contracted guinea pig hilar bronchi in vitro. In contrast,

20-hydroxyeicosatetraenoic acid caused contraction to near maximal tension. We conclude that CYP2B4, an abundant rabbit lung cytochrome P450 enzyme, is the primary constitutive pulmonary arachidonic acid epoxygenase and that these locally produced, biologically active eicosanoids may be involved in maintaining homeostasis within the lung.

L136 ANSWER 16 OF 25 MEDLINE on STN
ACCESSION NUMBER: 95142661 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7840649
TITLE: Metabolism of **epoxyeicosatrienoic** acids by cytosolic epoxide hydrolase: substrate structural determinants of asymmetric catalysis.
AUTHOR: **Zeldin D C**; Wei S; Falck J R; Hammock B D; Snapper J R; Capdevila J H
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee 37236.
CONTRACT NUMBER: ES02710 (NIEHS)
GM31278 (NIGMS)
GM37922 (NIGMS)
+
SOURCE: Archives of biochemistry and biophysics, **(1995 Jan 10)** 316 (1) 443-51.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19950314
Entered Medline: 19950302

AB The metabolism of cis-**epoxyeicosatrienoic** acids (**EETs**), methyl cis-**epoxyeicosatrienoates**, and cis-epoxyeicosanoic acids by cytosolic epoxide hydrolase was studied to identify substrate structural features important for stereoselective metabolism and chiral diol formation. 14(R), 15(S)-, 11(S),12(R)-, and 8(S),9(R)-**EET**, the predominant enantiomers present endogenously in rat organs, were metabolized at substantially higher rates than their antipodes. With the exception of 8(R),9(S)-**EET** (Km = 41 microM), differences in enantiomer hydration rates appear to be caused by Km-independent factors since the apparent Km values for the enantiomers of 14,15-, 11,12-, and 8(S),9(R)-**EET** were similar (between 3 and 5 microM). Chiral analysis of the diols resulting from enzymatic hydration of homochiral **EETs** showed that the regio and/or stereochemistry of water addition was **EET** regioisomer dependent. For the 11,12-**EET** enantiomers, water addition was nonregioselective; whereas, with both 8,9-**EET** antipodes water addition occurred predominantly at C9. Importantly, for 14,15-**EET** the regiochemistry of water addition was enantiomer-dependent. Only with 14(R),15(S)-**EET** did enzymatic hydration result in regiospecific addition at C15. Hence, enantioselective **EET** hydration is determined, principally, by enantiomer specific differences in rates of catalytic turnover and/or substrate binding parameters. On the other hand, the chirality of the diol products is determined by **EET** enantiomer-dependent differences in the regiochemistry of enzymatic oxirane cleavage and water addition. Esterification resulted in an overall reduction in the rates of epoxide hydration for all three **EET**-methyl esters (59, 89, and 68% of the **EET** rate for 8,9-, 11,12-, and 14,15-**EET**-methyl ester, respectively) and in the loss of regioselectivity during methyl 8(S),9(R)-**EET** oxirane

cleavage. Catalytic **EET** hydrogenation reduced the rates of **EET** hydration (56, 45, and 23% of the **EET** rates for 8,9-, 11,12-, and 14,15-epoxyeicosanoic acids, respectively). Compared to 14,15-**EET**, enzyme catalyzed hydration of 14,15-epoxyeicosanoic acid was less regioselective and yielded products with a substantially lower chiral purity. Based on these data, as well as on the documentation of 14(R),15(R)-**dihydroxyeicosatrienoic** acid as an endogenous constituent of rat urine we concluded that: (1) cytosolic epoxide hydrolase plays a significant role in the regio- and stereoselective metabolism of endogenous **EETs**; (2) differences in the affinities and/or turnover rates of the enzyme for the individual **EET** antipodes may be responsible for enantioselective **EET** metabolism; and (3) for 14,15- and 8,9-**EET**, regioselective and/or enantioselective oxirane water addition is responsible for asymmetric diol formation.(ABSTRACT TRUNCATED AT 400 WORDS)

L136 ANSWER 17 OF 25 MEDLINE on STN
ACCESSION NUMBER: 93203232 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8454612
TITLE: Regio- and enantiofacial selectivity of **epoxyeicosatrienoic** acid hydration by cytosolic epoxide hydrolase.
AUTHOR: **Zeldin D C**; Kobayashi J; Falck J R; Winder B S; Hammock B D; Snapper J R; Capdevila J H
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee 37232.
CONTRACT NUMBER: ES02710 (NIEHS)
GM37922 (NIGMS)
HL27274 (NHLBI)
+
SOURCE: Journal of biological chemistry, **(1993 Mar 25)** 268 (9) 6402-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19930507
Entered Medline: 19930422

AB The hydration of cis-**epoxyeicosatrienoic** acids to the corresponding vic-**dihydroxyeicosatrienoic** acids by cytosolic epoxide hydrolase demonstrates moderate regioselectivity with rates of hydration highest for the 14,15-epoxide and lower for the 11,12- and 8,9-epoxide (4.5, 1.6, and 1.5 mumol of product/mg of protein/min, respectively). Incubations of the 8,9- and 14,15-epoxides with cytosolic epoxide hydrolase show stereoselective formation of diols (7:3 and 4:1 ratio of antipodes, respectively) and concomitant chiral enrichment of the remaining unmetabolized substrate. In contrast, hydration of the 11,12-epoxide is nonenantioselective. The Km value of the enzyme for the 14(R),15(S)-epoxide is 3 microM. Incubations of the enantiomerically pure 8,9- and 14,15-epoxides with lung or liver cytosol, followed by chiral analysis of the resulting diols demonstrate selective cleavage of the oxirane ring at C9 and C15, respectively. On the other hand, cleavage of the 11,12- oxirane ring was less selective. The stereochemical preference of the cytosolic epoxide hydrolase, together with the known chiral composition of the endogenous arachidonate epoxide pools, suggests a functional role for this enzyme in the metabolism of these important compounds.

L136 ANSWER 18 OF 25 MEDLINE on STN
ACCESSION NUMBER: 93128576 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1481976
TITLE: Resolution of dihydroxyeicosanoates and of **dihydroxyeicosatrienoates** by chiral phase chromatography.
AUTHOR: Capdevila J H; Wei S; Kumar A; Kobayashi J; Snapper J R; **Zeldin D C**; Bhatt R K; Falck J R
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical School, Nashville, Tennessee 37232.
CONTRACT NUMBER: GM 31278 (NIGMS)
GM 37922 (NIGMS)
HLB 27274 (NHLBI)
+
SOURCE: Analytical biochemistry, **(1992 Dec)** 207 (2) 236-40.
Journal code: 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 19960129
Entered Medline: 19930211

AB A chromatographic method is described for the direct enantiomeric characterization of 5,6-, 8,9-, 11,12-, and 14,15-vic-**dihydroxyeicosatrienoic** acids (**DHETs**), metabolites of the cytochrome P-450 arachidonate epoxygenase pathway, and of their corresponding saturated vic-dihydroxyeicosanoic acids. Following esterification, the individual methyl or pentafluorobenzyl esters are resolved by chiral-phase chromatography utilizing a Chiralcel OC or OD column. This methodology will find analytical and preparative applications since it is simple and efficient and preserves, intact, the diol functionality.

L136 ANSWER 19 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999082763 EMBASE
TITLE: P450 subfamily CYP2J and their role in the bioactivation of arachidonic acid in extrahepatic tissues.
AUTHOR: Scarborough P.E.; Ma J.; Qu W.; **Zeldin D.C.**
CORPORATE SOURCE: D.C. Zeldin, Laboratory of Pulmonary Pathobiology, Natl. Inst. of Envtl. Hlth. Sciences, National Institutes of Health, Research Triangle Park, NC 27709, United States. zeldin@niehs.nih.gov
SOURCE: Drug Metabolism Reviews, (1999) 31/1 (205-234).
Refs: 89
ISSN: 0360-2532 CODEN: DMTRAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Several members of the CYP2J subfamily have been identified in rodents, although only a single gene has been identified in humans. The CYP2J cDNAs encode heme-thiolate proteins that bioactivate arachidonic acid and can also catalyze the metabolism of several xenobiotic substrates including benzophetamine, diclofenac, and bufuralol. The CYP2J are abundant in

extrahepatic tissues, including the heart and kidney, and within these organs, CYP2J expression is localized to specific cells. **EETs**, the major eicosanoid metabolites of the CYP2J enzymes, are endogenous constituents of tissues where CYP2J proteins are abundant and exhibit potent biological activities therein. The CYP2J isoforms appear to be regulated during development and in a tissue-specific fashion. Future studies should evaluate the effects of altered CYP2J protein expression on cell and organ function and elucidate the biochemical and molecular mechanisms involved in the regulation of the CYP2J enzymes.

L136 ANSWER 20 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:334771 BIOSIS
DOCUMENT NUMBER: PREV199800334771
TITLE: Dispartate effects of 11,12-**epoxyeicosatrienoic** acid (11,12-**EET**) and arachidonic acid (AA) in perfused and ischemic myocardium.
AUTHOR(S): Lane, C. J. [Reprint author]; Yang, H. [Reprint author]; Muller-Borer, B. J. [Reprint author]; **Zeldin, D. C.** ; Cascio, W. E. [Reprint author]
CORPORATE SOURCE: Univ. N.C., Chapel Hill, NC, USA
SOURCE: Biophysical Journal, (Feb., 1998) Vol. 74, No. 2 PART 2, pp. A161. print.
Meeting Info.: Forty-second Annual Meeting of the Biophysical Society. Kansas City, Missouri, USA. February 22-26, 1998.
CODEN: BIOJAU. ISSN: 0006-3495.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

QH505, A1
B537

L136 ANSWER 21 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1998:334454 BIOSIS
DOCUMENT NUMBER: PREV199800334454
TITLE: Inhibition of cardiac L-type calcium channels by **epoxyeicosatrienoic** acids.
AUTHOR(S): Chen, J. [Reprint author]; **Zeldin, D. C.**; Rosenberg, R. L. [Reprint author]
CORPORATE SOURCE: Dep. Physiol., Univ. North Carolina-Chapel Hill, Chapel Hill, NC 27599, USA
SOURCE: Biophysical Journal, (Feb., 1998) Vol. 74, No. 2 PART 2, pp. A105. print.
Meeting Info.: Forty-second Annual Meeting of the Biophysical Society. Kansas City, Missouri, USA. February 22-26, 1998.
CODEN: BIOJAU. ISSN: 0006-3495.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L136 ANSWER 22 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1994:518511 BIOSIS

DOCUMENT NUMBER: PREV199497531511
TITLE: Molecular cloning, expression and enzymatic characterization of a human kidney cytochrome P450 arachidonic acid epoxygenase.
AUTHOR(S): Capdevila, Jorge H.; Jacobson, Harry; **Zeldin, Darryl**
CORPORATE SOURCE: Dep. Med., Vanderbilt Univ., Nashville, TN, USA
SOURCE: Journal of the American Society of Nephrology, (1994) Vol. 5, No. 3, pp. 677.
Meeting Info.: Abstracts Submitted for the 27th Annual Meeting of the American Society of Nephrology. Orlando, Florida, USA. October 26-29, 1994.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 1994
Last Updated on STN: 3 Dec 1994

L136 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1992:317251 BIOSIS
DOCUMENT NUMBER: PREV199243017976; BR43:17976
TITLE: ENZYMATIC HYDRATION OF CIS **EPOXYEICOSATRIENOIC** ACIDS **EETS** BY RABBIT LUNG CYTOSOL.
AUTHOR(S): **ZELDIN D C** [Reprint author]; KOBAYASHI J; SNAPPER J R; CAPDEVILA J H
CORPORATE SOURCE: VANDERBILT UNIV MED CENT, NASHVILLE, TENN, USA
SOURCE: American Review of Respiratory Disease, (1992) Vol. 145, No. 4 PART 2, pp. A371.
Meeting Info.: 1992 INTERNATIONAL CONFERENCE OF THE AMERICAN LUNG ASSOCIATION AND THE AMERICAN THORACIC SOCIETY, MIAMI BEACH, FLORIDA, USA, MAY 17-20, 1992. AM REV RESPIR DIS.
CODEN: ARDSBL. ISSN: 0003-0805.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 30 Jun 1992
Last Updated on STN: 30 Jun 1992

L136 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:197917 HCAPLUS
DOCUMENT NUMBER: 138:231736
TITLE: Inhibitors of epoxide hydrolases for the treatment of hypertension
INVENTOR(S): Kroetz, Deanna L.; **Zeldin, Darryl C.**; Hammock, Bruce D.; Morisseau, Christophe
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: U.S., 36 pp., Cont.-in-part of U.S. 6,150,415.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6531506	B1	20030311	US 2000-721261	20001121
US 5955496	A	19990921	US 1997-909523	19970812 <--

US 6150415	A	20001121	US 1999-252148	19990218
US 2003119900	A1	20030626	US 2002-328495	20021223
US 6693130	B2	20040217		
US 2004092487	A1	20040513	US 2003-694641	20031027
PRIORITY APPLN. INFO.:			US 1996-23397P	P 19960813
			US 1997-909523	A2 19970812
			US 1999-252148	A2 19990218
			US 2000-721261	A1 20001121
			US 2002-328495	A1 20021223

OTHER SOURCE(S): MARPAT 138:231736
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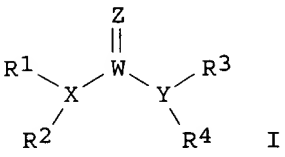

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AB The invention provides compds. that inhibit epoxide hydrolase in therapeutic applications for the treatment of hypertension. A preferred class of compds. for practicing the invention have the structure shown by Formula [(R1)(R2)XW(Z)Y(R3)(R4)], wherein Z is oxygen or sulfur, W is carbon phosphorous or sulfur, X and Y is each independently nitrogen, oxygen, or sulfur, and X can further be carbon, at least one of R1-R4 is hydrogen, R2 is hydrogen when X is nitrogen but is not present when X is sulfur or oxygen, R4 is hydrogen when Y is nitrogen but is not present when Y is sulfur or oxygen, R1 and R3 is each independently C1-C20 substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, or heterocyclic.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:234369 HCAPLUS
DOCUMENT NUMBER: 133:13051
TITLE: **Epoxyeicosatrienoic** acids potentiate Ca2+ signaling in both endothelial and vascular smooth muscle cells
AUTHOR(S): Mombouli, Jean-Vivien; **Zeldin, Darryl**; Scott-Burden, Timothy; Holzmann, Sigrid; Kostner, Gert M.; Graier, Wolfgang F.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Endothelium-Dependent Hyperpolarizations, [Proceedings of the International Symposium on Endothelium-Derived Hyperpolarizing Factor], 2nd, Vaux de Cernay, France, June 5-6, 1998 (**1999**), Meeting Date 1998, 77-83. Editor(s): Vanhoutte, Paul M. Harwood Academic Publishers: Amsterdam, Neth.
CODEN: 68TZAU
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Expts. were designed to assess the impact on Ca2+ signaling of sustained increases in the concentration **epoxyeicosatrienoic** acids (**EETs**) in cultured endothelial or vascular smooth muscle cells. Cultured human umbilical vein-derived endothelial cells (EA.hy926) and bovine aortic vascular smooth muscle cells were processed for conventional spectrofluorometric measurement of cytosolic Ca2+, using Fura 2/AM. A

bovine aortic vascular smooth muscle cell line expressing the CYP2J2 epoxygenase was developed to determine the impact of chronic enhancement of epoxygenase activity. In EA.hy926 endothelial cells, the histamine-induced mobilization of Ca2+ from intracellular stores, as well as the stimulation of Ca2+ influx were inhibited by the cytochrome P 450 inhibitor thiopental. However, incubation of the cells with 11,12-**EET** amplified the mobilization of Ca2+ from both intracellular and extracellular pools. In this case, thiopental no longer affects significantly the mobilization of Ca2+ induced by histamine in EA.hy926 cells. A similar potentiation of Ca2+ signaling was obtained in bovine aortic vascular smooth muscle cells stimulated with thapsigargin. In vascular smooth muscle cells overexpressing the epoxygenase CYP2J2, an increased spontaneous Ca2+ influx was obtained, as well as an amplification of endothelin 1-induced capacitative Ca2+ entry. These results show that sustained increases in **EET** levels result in an amplification of the mobilization of cytosolic Ca2+ in cultured endothelial and vascular smooth muscle cells.

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